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PATHOGENETIC MECHANISMS IN HEMOLYTIC ANEMIAS

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Because of the finding of hemolysins of the immune body type in 2 cases of acute (acquired) hemolytic anemia and because of their disappearance as the patients improved after splenectomy, the possibility was conceived that a hemolysin might be directly related to the development of the hemolytic process.[1] Immune hemolytic serum, produced in rabbits by the injection of guinea pig erythrocytes, when injected in guinea pigs resulted in fulminating, acute and subacute hemolytic states dependent on the dose of serum injected.[2] In both clinical patients and experimental animals spherocytosis and increased fragility of the erythrocytes in hypotonic solutions of sodium chloride were present and regressed as the process improved. It was concluded (*a*) that hemolytic anemias are due to the activity of agents which can be generically called hemolysins and (*b*) that spherocytosis (and increased hypotonic fragility) are the result of the activity of various types of hemolytic agents; thus spherocytosis can be considered an indicator of the presence of hemolytic activity.

More recently, Ham and Castle [3] proposed another explanation for the development of hemolytic anemia clinically and for our results with the use of immune hemolytic serum experimentally. Their explanation is based on the theory that unusual erythrostasis—as the result of agglutination, increased viscosity or slowing of the circulation—is at the basis of many hemolytic processes. Our results [2] in experimental animals were explained by these investigators by the action of "agglutinating antibodies" in the hemolytic serum, the erythrocytes becoming agglutinated, with resultant stasis and hemolysis. That erythrocytes could be *directly* injured by the activity of various hemolytic or agglutinating agents was not seriously considered.

Our recent experiments indicate that the erythrocyte—normally a biconcave disk—is actively injured by a variety of agents, "simple" hemolysins, "complex" hemolysins or simple agglutinins, with the result that it is rendered susceptible to

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From the Joseph H. Pratt Diagnostic Hospital and the Blood Clinic and Laboratory of the Boston Dispensary.

Read before the Section on Pathology and Physiology at the Ninety-Second Annual Session of the American Medical Association, Cleveland, June 6, 1941.

1. Dameshek, W., and Schwartz, S. O.: The Presence of Hemolysins in Acute Hemolytic Anemia, New England J. Med. **218**:75, 1938.

2. Dameshek, W., and Schwartz, S. O.: Hemolysins as the Cause of Clinical and Experimental Hemolytic Anemias, Am. J. M. Sc. **196**:769, 1938.

3. Ham, T. H., and Castle, W. B.: Studies on Destruction of Red Blood Cells: Relation of Increased Hypotonic Fragility and of Erythrostasis to the Mechanism of Hemolysis in Certain Anemias, Tr. A. Am. Physicians **55**:127, 1940.

such major factors as complement activity and mechanical trauma. Whereas in the experiments of Ham and Castle the emphasis was on the passive factor of stasis, our past and recent experiments have stressed the multiplicity of agents—immunologic, chemical and physical—which may actively injure the envelope of the red cell. The exact role of the spleen in hemolytic anemia is still obscure, although our experience in certain clinical cases suggests that it may directly produce hemolysins rather than act as a simple mechanical organ of stasis. Active extrasplenic production of hemolysins is also probable in certain cases of "symptomatic" hemolytic anemia.[4]

In the present paper the role of various factors in the development of hemolysins is described. The activities of a pure hemolysin (saponin), of a pure agglutinin (concanavalin A) and of complex hemolysins (immune hemolytic serum and silicic acid) have been studied with relation to stasis, mechanical fragility and hypotonic fragility, and the effects in experimental animals noted. From the results of these experiments and other data, a formulation of etiologic factors which may underlie the various hemolytic syndromes has been made.

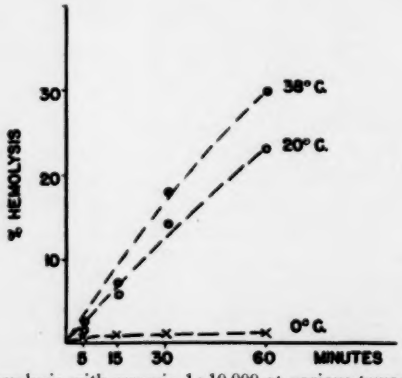

Fig. 1.—Rate of hemolysis with saponin 1: 10,000 at various temperatures. Saponin, a simple hemolysin, causes hemolysis without the aid of other factors. Hemolysis is greatest at incubator temperature and practically nil at refrigerator temperature.

EXPERIMENTAL OBSERVATIONS

1. Saponin, a Simple Hemolysin.—Purified saponin (Merck), a powder, was dissolved in physiologic solution of sodium chloride, a 1: 10,000 concentration ordinarily being used. When this was kept in the refrigerator, a standard hemolytic activity against suspensions of human red cells containing 20,000,000 washed red cells per cubic centimeter of physiologic solution of sodium chloride was present for at least two weeks, although the precaution was observed of making up solutions at weekly intervals. The rate and degree of hemolysis were observed by use of the Evelyn photoelectric colorimeter.

The experiments were in general confirmatory of Ponder's [5] extensive experiments with this substance. They showed that saponin acts directly on the erythrocyte without mediation of complement or other substances present in serum, that hemolysis is most marked at incubator temperature (fig. 1) and that spherocytosis with greatly increased hypotonic fragility is present at subhemolytic levels of saponin concentration. When the material was injected intravenously in rabbits in large doses, an acute hemolytic anemia with marked spherocytosis resulted, due apparently to the direct action of the drug on circulating erythrocytes.

2. Silicic Acid, a Complex Hemolysin.—Silicic acid was prepared by distillation from ethyl silicate. One cubic centimeter of the heavy grayish liquid was mixed with 24 cc. of distilled

4. Singer, K., and Dameshek, W.: Symptomatic Hemolytic Anemia, Ann. Int. Med. **15**:544, 1941.

5. Ponder, E.: Effects of Simple Haemolysins in Hypotonic Systems, Protoplasma **27**: 523, 1937.

water in a flask, heated directly over a small flame for hydrolysis and distilled for two hours in a reflux condenser. The silicic acid thus obtained was stored in the ice box. One cubic centimeter of this solution was mixed with 0.085 cc. of a 10 per cent solution of sodium chloride and diluted in varying concentrations, 1:10, 1:20, etc., with physiologic solution of sodium chloride. The final dilutions, labeled 1:10, etc., were used in the experiments, to be described, against guinea pig red blood cells. Blood was obtained from guinea pigs by puncture of the heart. It was washed three times with physiologic solution of sodium chloride and suspended in 10 per cent concentration. Occasionally a 5 per cent suspension was used. Fresh guinea pig complement in 1:10 dilution was routinely used. The tests for hemolysis were usually performed in Hinton tubes (4 by ⅜ inches [10 by 0.95 cm.]). The degree of hemolysis was determined by inverting the tubes once, centrifuging them for five minutes at high speed, removing 3 cc. of the supernatant fluid, diluting this with 17 cc. of 0.1 per cent solution of sodium carbonate and reading the Cenco photoelectric colorimeter for hemoglobin concentration, Cenco green filter no. 2 being utilized. The degree of hemolysis was readily ascertained from the hemoglobin reading.

General Results: Silicic acid caused marked agglutination of guinea pig red cells in concentrations of 1:10 to 1:10,000. On the addition of guinea pig complement (1:10) to the agglutinated red cells, hemolysis took place immediately at the boundary between the complement and the red cells and gradually extended to the rest of the tube. Hemolysis was facilitated by incubation at 38 C. and diminished at ice box temperature (0 C.), as shown in figures 2 and 3.

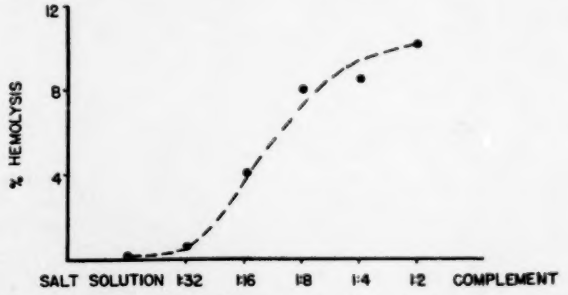

Fig. 2.—Hemolysis with colloidal silicic acid with added complement in various concentrations. Silicic acid, a complex hemolysin, without complement causes agglutination; with added guinea pig complement the degree of hemolysis is directly dependent on the concentration of complement. Complement is the actual hemolytic agent of cells already sensitized by silicic acid.

Effects of Stasis on Sensitized Erythrocytes: Erythrocytes sensitized (i. e., agglutinated) by various concentrations of silicic acid (without complement) were observed at different temperatures for various periods and the degree of hemolysis noted. Although the results of these experiments varied from time to time, it was found that silicic acid in 1:10, 1:100, 1:1,000 and 1:10,000 concentrations caused agglutination of guinea pig red cells. When these cells were allowed to stand for forty-two hours at ice box temperature no hemolysis occurred; at room temperature for the same length of time there was questionable hemolysis, while at incubator temperature well marked hemolysis took place in the 1:10 concentration of silicic acid. There was slight hemolysis in the 1:100 concentration, but in the 1:1,000 and 1:10,000 concentrations there appeared to be an inhibition of hemolysis as compared with that of the control.

In other experiments, no essential change between the degree of hemolysis in the controls and in the sensitized cells occurred for seventeen and one-half hours, but at the nineteen hour interval a definite and well marked increase in hemolysis took place (fig. 4), particularly in the higher concentrations. Suspensions of red cells made with isotonic 5.2 per cent dextrose solution instead of physiologic solution of sodium chloride showed definitely diminished hemolysis with stasis.

Effect on Hypotonic Fragility: Erythrocytes sensitized (complement not used) by silicic acid were tested for their fragility in hypotonic solutions of sodium chloride. In one experiment, 12 cc. of 1:100 silicic acid, 12 cc. of 1:10 suspension of guinea pig red cells and 36 cc. of physiologic solution of sodium chloride were mixed, the tubes inverted once, the agglutinated masses of red cells discarded, the rest of the red cell suspension centrifugated at low speed

for five minutes and the cells washed three times and then tested for hypotonic fragility by the method of Daland and Worthley.[6] There was no definite increase in hypotonic fragility (hemolysis, 0.46 to 0.12 per cent) with this method over that of control (0.42 to 0.22 per cent). The method was, however, open to question because the agglutinated red cells were discarded.

In another experiment, the fragility test with hypotonic solutions showed hemolysis of normal unsensitized guinea pig erythrocytes to begin at 0.44 and end at 0.28 per cent. Erythrocytes sensitized by silicic acid (5 cc. of a 10 per cent suspension of guinea pig red

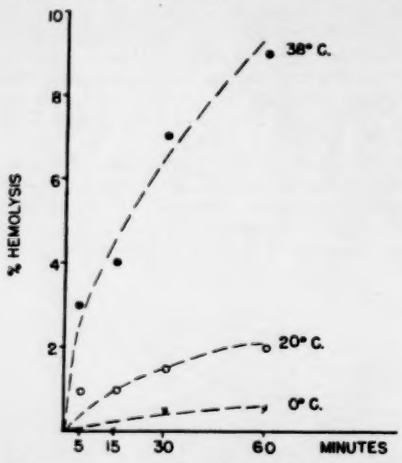

Fig. 3.—Rate of hemolysis with colloidal silicic acid 1: 5 with added complement. Temperature is a factor in the degree of hemolysis in a colloidal silicic acid–complement system. The greatest hemolysis occurs at incubator temperature and very little at refrigerator temperature. This indicates that the reaction is to some extent a metabolic one.

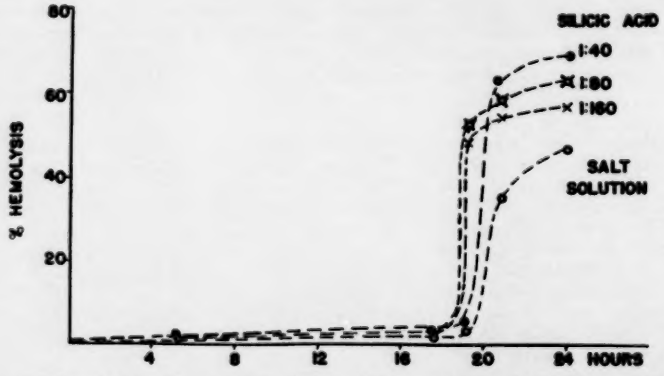

Fig. 4.—Hemolysis with colloidal silicic acid in various concentrations; stasis at 38 C. Erythrostasis of red cells agglutinated by silicic acid failed to result in hemolysis for eighteen hours; at the end of that time, a sharp increase in hemolysis took place, greatest with the cells agglutinated by the highest (1: 40) concentration of silicic acid. It should be noted, however, that the normal control red cells also became moderately hemolyzed after twenty hours' incubation.

6. Daland, G. A., and Worthley, K.: The Resistance of Red Blood Cells to Hemolysis in Hypotonic Solutions of Sodium Chloride, J. Lab. & Clin. Med. **20**:1122, 1935.

cells, 5 cc. of 1:10 silicic acid and 15 cc. of physiologic solution of sodium chloride) were allowed to settle in large Evelyn tubes. The supernatant fluid was then drawn off and fresh saline solution added three times and drawn off from the sedimented red cells. After the last withdrawal, 1 drop of sedimented red cells was added to each of various concentrations of hypotonic solution of sodium chloride. By this method hemolysis began at 0.68 and ended at 0.20 per cent, a definite change. In a similar experiment, the hypotonic fragility became modified, hemolysis occurring at first between 0.44 and 0.16 and then between 0.60 and 0.16 per cent.

Effect of Mechanical Trauma (Shaking): Different concentrations of silicic acid were mixed with standard suspensions of guinea pig red cells and physiologic solution of sodium chloride in Hinton tubes. Six glass beads (approximately 3 mm. in diameter) were added

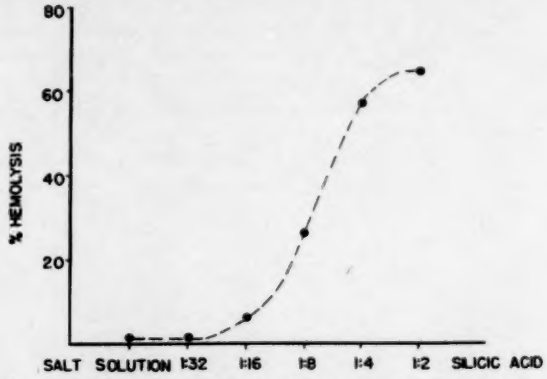

Fig. 5.—Hemolysis with colloidal silicic acid; mechanical fragility (shaking three hours); use of various concentrations. The degree of hemolysis of red cells treated with colloidal silicic acid and then shaken with glass beads varied directly with the concentration of silicic acid used.

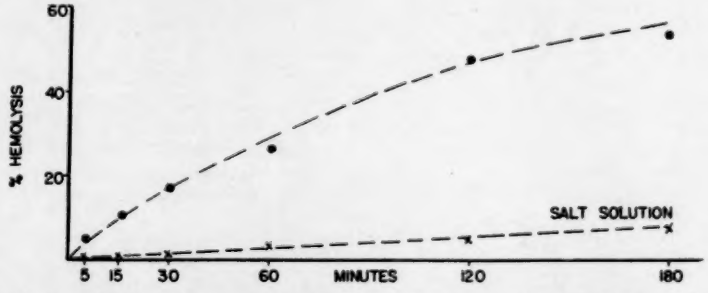

Fig. 6.—Hemolysis with colloidal silicic acid 1:10; mechanical fragility (shaking three hours). Red cells acted on by silicic acid without complement were readily hemolyzed by mechanical trauma (shaking with glass beads), normal red cells being only slightly affected.

to each tube, and the tubes were placed on a mechanical pipet shaker and shaken for three hours. At the end of this time, the tubes were centrifuged at low speed for three minutes, and 3 cc. of the supernatant fluid was removed and added to 17 cc. of a 0.1 per cent solution of sodium carbonate. The degree of hemolysis was read as hemoglobin with the Cenco photoelectric colorimeter. There was marked hemolysis with the highest concentrations of silicic acid (fig. 5). The degree of hemolysis varied directly with the time of shaking, most taking place in the first fifteen minutes (fig. 6). When the red cells were incubated at 37 C. for one hour after "sensitization" and then shaken for one hour, there was a slight increase in the degree of hemolysis, but when red cells were first

allowed to stand for one and one-half hours at refrigerator temperature, a definite decrease in hemolysis with shaking took place (fig. 7).

Animal Experiments: Undiluted silicic acid was injected intraperitoneally daily into a guinea pig and frequent observations made of the hemoglobin, red blood cell count, white blood cell count, blood smears and hypotonic fragility. No essential changes in the values occurred during the period of injections (Dec. 4-11, 1941), although doses of 3 cc. each were given on the last two days.

Increasing doses (0.5 to 4 cc.) of undiluted silicic acid were injected intravenously for five days into a rabbit without change in values for hemoglobin, red blood cell count or hypotonic fragility. Moderate leukocytosis (up to 34,500 leukocytes per cubic millimeter) developed.

In view of these negative results, further in vivo experiments were considered inadvisable.

Silicic acid, like tannic acid and other inorganic substances studied by Landsteiner and Jagic,[7] Landsteiner and Rock,[8] Reiner and Fischer[9] and Ponder,[5] exhibits unusually interesting results in relation to complement activity. Without complement there is marked agglutination of red cell suspensions; with complement hemolysis rapidly occurs. Like immune hemolytic serum, this substance may thus be called a complex hemolysin, and its interesting activities together with their significance are discussed in the next part of the paper.

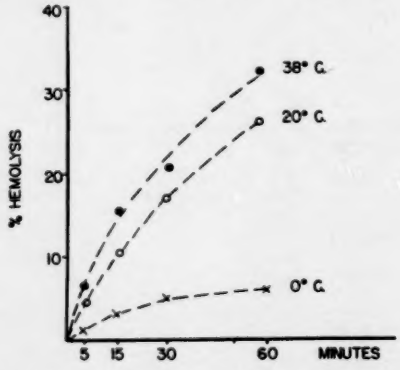

Fig. 7.—Hemolysis with colloidal silicic acid 1:10; stasis at various temperatures for one hour before shaking. That the degree of hemolysis with shaking was to some extent associated with metabolic changes in the red cells is evident from the fact that stasis for one hour at incubator temperature prior to shaking increased the mechanical fragility, whereas keeping the red cells at refrigerator temperature diminished the mechanical fragility.

3. Immune Hemolytic Serum, a Complex Hemolysin.—Immune heterohemolytic serum was prepared, as in previous experiments,[2] by injecting guinea pig erythrocytes intravenously into rabbits and after appropriate intervals removing blood from the rabbits. The serum thus obtained possessed both agglutinative and hemolytic activities against normal guinea pig red cells in vitro and when the dose was varied produced hemolytic anemia of varying degrees when injected in vivo. In the in vitro experiments, a serum with a hemolytic titer of 1:64 was routinely used together with 5 or 10 per cent suspensions of guinea pig erythrocytes and fresh guinea pig complement, usually in 10 per cent dilution.

7. Landsteiner, K., and Jagic, N.: Ueber die Verbindungen und die Entstehung von Immunkörpern, München. med. Wchnschr. **50**:764, 1903.

8. Landsteiner, K., and Rock, H.: Untersuchungen über Komplementwirkung. Hämolyse durch Kieselsäure und Komplement, Ztschr. f. Immunitätsforsch. u. exper. Therap. **14**: 14, 1912.

9. Reiner, L., and Fischer, O.: Beiträge zum Mechanismus der Immunkörperwirkung. Ztschr. f. Immunitätsforsch. u. exper. Therap. **61**:317, 1929.

General Results: Immune hemolytic serum, "inactivated" by heating for one hour at 56 C., caused agglutination of guinea pig erythrocytes in high titer but no hemolysis. With guinea pig complement present, there was complete hemolysis with the serum used to a titer of 1:64 after one hour's incubation at 37 C. Doubling the amount of complement, considerably increased the hemolytic titer. Thus, complement was the actual hemolyzing agent, although it could not act on already fully agglutinated red cells.

The rate of hemolysis in the complete hemolytic system was in some measure dependent on the temperature. The most marked degrees of hemolysis took place at incubator temperature and the least at refrigerator levels (fig. 8).

Effects of Stasis on Sensitized (Agglutinated) Red Cells (Without Complement): Inactivated immune serum (without added complement) with a titer of 1:64 was diluted to various concentrations (1:128, 1:256 and 1:512) and mixed with 10 per cent guinea pig erythrocytes and physiologic solution of sodium chloride. The tubes were inverted once and placed in the incubator at 38 C. for periods varying from five and one-half to eighty-nine hours. At the sixteen and nineteen hour periods the control tubes showed more marked hemolysis than those containing immune serum. In another experiment of this type, with somewhat different concentrations of immune serum (1:25, 1:50, 1:100 and 1:200) there was definitely more hemolysis in the control red cells than in those which were sensitized (agglutinated). Cells treated with 1:400, 1:800 and 1:1,600 dilutions of serum behaved like normal erythrocytes in one experiment but showed distinctly less hemolysis than the controls

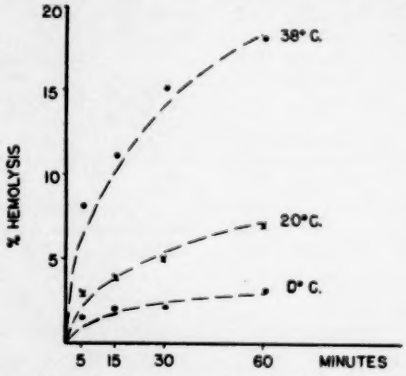

Fig. 8.—Rate of hemolysis with immune hemolytic serum 1:25 with added complement. Immune hemolytic serum, like silicic acid, results in agglutination without complement; complement is the actual hemolyzing agent; the activity of complement is greatest at incubator temperature and minimal at refrigerator temperature.

in an experiment with incubation at 24 C. (fig. 9). Thus, in all these experiments, the cells which were sensitized by immune serum appeared to be less liable to hemolysis by stasis than normal cells. This finding differed somewhat from the results of similar experiments with silicic acid (already described) and was thought to be due to the greater degree of agglutination (often in one solid button) by immune serum. To avoid this, very dilute concentrations of immune serum were used again, but with similar results.

Effects on Hypotonic Fragility: Experiments to show the effect of immune serum on the hypotonic fragility of erythrocytes were for the most part unsatisfactory. If guinea pig complement was used, even the slight degree of hemolysis present at high dilutions of serum was usually sufficient to cause difficulty in reading the results. If complement was not added, marked agglutination took place; the agglutinated masses of red cells could then be either discarded or tested. If discarded, they might represent the injured red cells; if tested, their agglutination in masses might be a deterrent to the action of hypotonic solution of sodium chloride. Various methods were utilized in the attempt to avoid these difficulties, but only the last one used was moderately conclusive.

In this method, 5 cc. of a 1:100 dilution of immune serum was mixed with 5 cc. of a 10 per cent suspension of guinea pig red cells, 5 cc. of 1:10 guinea pig complement and 10 cc of physiologic solution of sodium chloride; the cells were allowed to settle and were washed three times (not centrifuged), and the hypotonic fragility was determined in the

usual manner. With this method hemolysis of the sensitized red cells began at 0.60 per cent sodium chloride and was incomplete at 0.04 per cent. Hemolysis of the normal red cells in this experiment began at 0.44 and ended at 0.24 per cent; that of red cells allowed to stand at room temperature for eight hours and then overnight in the refrigerator at 0.46 and 0.22 per cent; that of cells incubated for one hour at 37 C., at 0.48 and 0.20 per cent, and that of cells sensitized (agglutinated) by immune inactivated serum without added complement, at 0.48 and 0.04 per cent.

Although this method offered certain advantages over that in which the cells—during the triple washing process—were centrifuged three times and although the hypotonic fragility was unquestionably increased, no definite conclusions could be drawn because of the possibility that the presence of complement resulted in some hemolysis. However, no trace of hemolysis

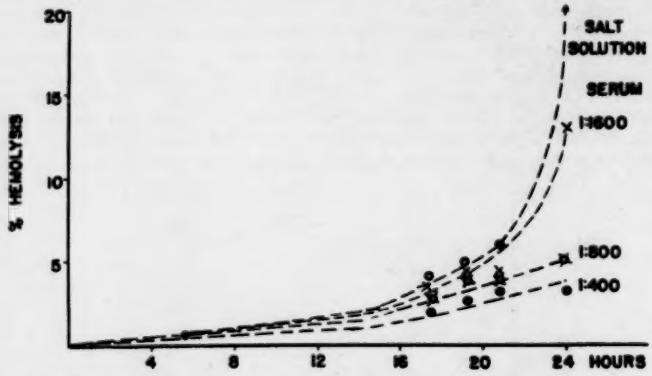

Fig. 9.—Hemolysis with immune hemolytic serum in various concentrations; stasis at 38 C. Stasis of red cells agglutinated by immune hemolytic serum without added complement resulted in distinctly less hemolysis than that of control red cells.

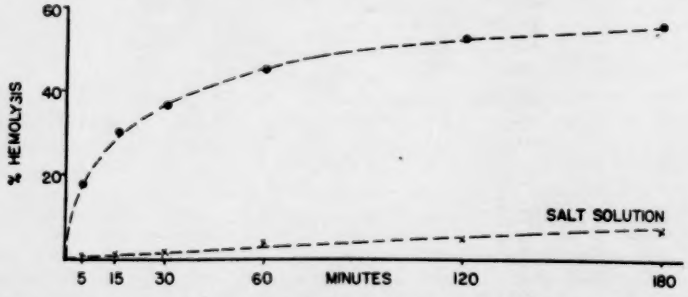

Fig. 10.—Hemolysis with immune hemolytic serum 1:4; mechanical fragility (shaking three hours). Red cells acted on by immune hemolytic serum when shaken with glass beads were to a large extent hemolyzed, the greatest hemolysis taking place in the first thirty minutes of shaking. Control red cells were only slightly affected by this form of mechanical trauma. As with silicic acid (fig. 5), the degree of hemolysis varied directly with the concentration (titer) of serum used.

was present in the tubes holding concentrations of sodium chloride from 0.80 to 0.64 per cent, inclusive, although definite hemolysis was present in the lower concentrations.

Effects on Mechanical Fragility: Numerous experiments performed on the mechanical fragility of erythrocytes sensitized by immune serum demonstrated a uniformly marked hemolytic effect. The experiments were usually performed by mixing 1 cc. of a dilution of inactivated immune serum with 1 cc. of a 10 per cent suspension of guinea pig red cells and 3 cc. of physiologic solution of sodium chloride in Hinton tubes, as previously described.

The degree of hemolysis with mechanical trauma varied directly with the concentration of immune serum and with the time of shaking (fig. 10). In one experiment 55 per cent of the total hemolysis induced by three hours' shaking took place in the first fifteen minutes. The degree of hemolysis induced by shaking, with the use of very dilute serums, could be considerably enhanced by incubating the mixture of immune serum, red cells and saline solution for one hour at 37 C. before shaking it.

Spherocytes, produced by injecting immune hemolytic serum into guinea pigs, when shaken for three to six hours showed no difference in mechanical fragility as compared with control red cells, although their hypotonic fragility was greatly altered. In an experiment of this type, acute hemolytic anemia (hemoglobin 9.7 Gm., red blood cells 3,670,000) was produced in a guinea pig by injection of hemolytic serum. There was spherocytosis, and hemolysis began at 0.72 and ended at 0.16 per cent sodium chloride. A 10 per cent suspension of cells from this guinea pig was shaken for three hours and compared with red cells from a guinea pig with a hemoglobin content of 14.5 Gm., a red cell count of 6,110,000 and hemolysis between 0.40 and 0.24 per cent sodium chloride. At the end of three hours of shaking, the degree of hemolysis was the same in both tubes, 3 per cent.

Effects on Morphologic Appearance of Red Cells: Various dilutions of serum with and without complement were mixed with guinea pig red cells and incubated at 38 C. for one hour (1 cc. of serum dilution, 1 cc. of 10 per cent guinea pig complement, 1 cc. of a 10 per cent suspension of guinea pig red cells and 2 cc. of physiologic solution of sodium chloride). At the end of the hour, the tubes were inverted once for mixing and a drop of each dilution was placed on a slide and examined under a cover slip with high magnification dry and oil immersion lenses. With the higher concentrations (1:30 and 1:60) of serum without complement, there was agglutination with "thorn apple deformity" (fig. 11 *A*); in the presence of complement, no thorn apple forms were present, but there were definite spherocytosis and poor rouleau formation with thickened red cells (fig. 11 *B*). Control red cells showed crenation, which could readily be discriminated from thorn apple deformity, and either questionable spherocytosis or no spherocytosis.

Animal Experiments: These have already been described.[2] The injection into guinea pigs of large doses (0.5 to 1 cc.) of immune hemolytic serum intraperitoneally was followed by a fulminating hemolytic anemia characterized by extreme spherocytosis, increased hypotonic fragility, hemoglobinuria and quick death. Moderate doses given intraperotineally daily resulted in acute hemolytic anemia, and small doses (0.1 cc.) given daily produced a subacute type of anemia with moderate spherocytosis, marked reticulocytosis, "pseudomacrocytosis" and only a slight change in hypotonic fragility.

Immune hemolytic serum, like silicic acid, is a complex hemolysin. The greatest effects on hemolysis in vitro, as with silicic acid, were obtained with either mechanical trauma or complement activity. Although erythrostasis for short periods might be important in enhancing the effects of both complement activity and mechanical trauma, stasis alone appeared to have little effect on sensitized (agglutinated) red cells. Thus, although the hypotonic fragility of red cells acted on by immune body might not be significantly altered, some change in the colloidal nature of the erythrocyte and/or its envelope appeared likely, since it became readily hemolyzed (*a*) by complement and (*b*) by mechanical injury.

4. Concanavalin A, a Pure Agglutinin.—Ham and Castle used concanavalin A, a crystalline protein (globulin) derived from the jack bean,[10] to produce agglutination of red cells in vitro and hemolytic anemia, presumably by agglutination effects, in the experimental animal. We obtained some of this material from J. B. Sumner in 9.6 per cent concentration dissolved in a saturated solution of sodium chloride.

For experimental use, 0.1 cc. (containing 9.6 mg.) of the saturated solution was diluted to isotonicity by the addition of 4.1 cc. of physiologic solution of sodium chloride. Dilutions of the isotonic solution with further amounts of the saline solution were labeled 1:10, etc. Experiments with guinea pig red cells, complement, stasis and mechanical fragility were carried out by the same technics as with silicic acid and immune hemolytic serum.

General Results: Concanavalin A is an extremely potent agglutinin of the erythrocytes of the guinea pig, of the rabbit and of the dog but not of the human being. In isotonic solution of sodium chloride, i. e. in a concentration of 230 mg. per hundred cubic centimeters,

10. Sumner, J. B., and Howell, S. F.: The Identification of the Hemagglutinin of the Jack Bean with Concanavalin A, J. Bact. **32**:227, 1936.

it caused extreme agglutination of 10 per cent suspension of guinea pig red cells in all dilutions up to approximately 1:10,000. The addition of guinea pig complement in different amounts to the various concentrations failed to cause any trace of hemolysis. Incubation with complement for one hour at 38 C. also failed to cause hemolysis. Thus, concanavalin A is a pure agglutinin, differing from the agglutinins silicic acid and immune serum which not only result in agglutination but facilitate hemolysis by complement.

The Effects of Stasis: Different concentrations (1:10 to 1:100,000) of isotonic solution of concanavalin A in 1 cc. amounts were mixed with 1 cc. of 10 per cent suspension of guinea pig red cells and 3 cc. of physiologic solution of sodium chloride in Hinton tubes and allowed to stand for periods varying from three to twenty-four hours in a water bath

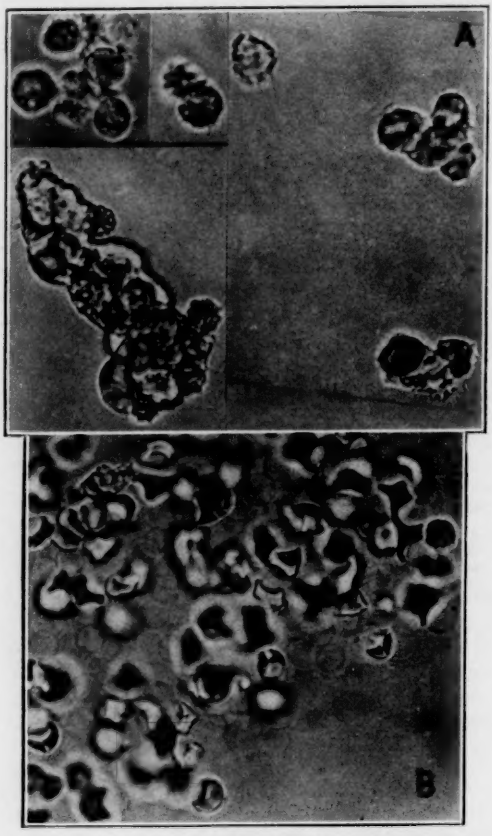

Fig. 11.—Red cells in contact with hemolytic serum from rabbits inoculated with guinea pig red blood cells. *A*, without added complement. Note the agglutination phenomena and the thorn apple appearance of the red blood cells. *B*, with added complement. Many of the red cells are almost completely hemolyzed. There is little thorn apple appearance. The red cells tend to be spherocytic and to form bizarre rouleaux.

at 37 C. The degree of hemolysis varied from experiment to experiment directly with the concentration used and the time of stasis. The greatest degrees of hemolysis were present with the highest concentrations of concanavalin A and the longest periods of incubation. When care was taken to avoid agglutination on the sides of the tubes by transferring the agglutinated red cells to other tubes, the degree of hemolysis was distinctly less than when this precaution was not observed; in fact, in one such experiment, there appeared to be actual inhibition of hemolysis (fig. 12).

The greatest degrees of hemolysis, as with silicic acid and immune hemolytic serum, were present at incubator temperature; keeping the agglutinated cells at ice box temperature effectively inhibited the hemolytic tendency; at room temperature, various degrees of hemolysis took place.

The results with stasis thus varied from experiment to experiment and appeared to depend to some degree on the extent of agglutination on the sides of the tubes and on the reaction of the agglutinated cells with the water of condensation. It was therefore impossible to draw any definite conclusion regarding the effect of erythrostasis on the agglutinated red cells.

The Effects on Hypotonic Fragility: Cells agglutinated by concanavalin A in various concentrations of distilled water to which was added hypotonic solution of sodium chloride failed to be hemolyzed, which shows that such cells are unusually resistant. However, in experiments in which the same technic was used as that employed with immune hemolytic serum, in which the agglutinated red cells were allowed slowly to settle and were washed three times (without centrifugation), there was a definite although slight increase in hypotonic fragility (hemolysis, between 0.38 and 0.20 to between 0.52 and 0.04 per cent), indicating again—as with silicic acid and immune hemolytic serum—that the process of agglutination effected some injury to the envelope of the erythrocyte and an increase in spheroidicity of the cell itself.

The Effects of Mechanical Trauma: The most marked and most consistent results were obtained with the trauma obtained by shaking the red cells with glass beads. The same

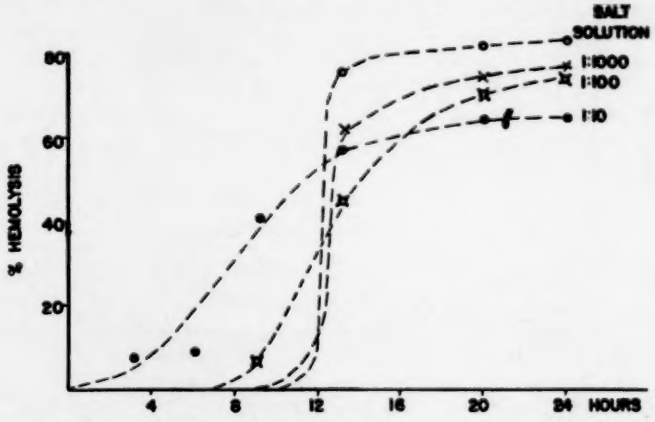

Fig. 12.—Hemolysis with concanavalin A in various concentrations; stasis at 38 C. Concanavalin A, a pure agglutinin, results only in agglutination even with added complement. Stasis of red cells agglutinated by concanavalin A resulted in a certain degree of hemolysis occurring prior to that of normal red cells; at twelve hours and thereafter, however, there was more hemolysis of the control red cells than of those affected by concanavalin A.

technic was utilized as with silicic acid and immune serum. As with these substances, the most marked hemolysis took place with the highest concentration of concanavalin A (1:10) and with the most shaking (fig. 13). However, by far the greatest amount of hemolysis (approximately 50 per cent of the total) took place within the first fifteen minutes of shaking. Somewhat more hemolysis took place if the agglutinated red cells were allowed to incubate for one hour prior to being shaken.

Animal Experiments: Guinea pigs inoculated intraperitoneally with undiluted and diluted concanavalin A died with marked abdominal distention and without the development of hemolytic anemia or spherocytosis. On the other hand, as Castle and Ham have already shown, in rabbits inoculated intravenously with concanavalin A acute hemolytic anemia developed, with spherocytosis and increased hypotonic fragility. This indicated that a pure agglutinin could produce hemolytic anemia only when intravascular agglutination could be produced.

Concanavalin A, a pure agglutinin, unlike the complex agglutinin hemolysins silicic acid and immune hemolytic serum, produces only agglutination; complement is without further effect. However, like the more complex substances studied, it

produces definite alterations of the envelope of the red cell. This is demonstrated by a slight alteration in hypotonic fragility and a marked alteration in the mechanical fragility, the reaction to erythrostasis being equivocal. When injected directly into the circulation, concanavalin A caused spherocytosis and hemolytic anemia, presumably as the result of intravascular agglutination.

COMMENT

The experiments described demonstrate that hemolysis of the red cell may be accomplished by pure or simple hemolysins (such as saponin), by complex hemolysins or agglutinins (silicic acid and immune hemolytic serum) and by pure agglutinins (such as concanavalin A). Saponin hemolyzes the red cell directly without the mediation of other factors, but the complex hemolysins and the agglutinins may require for hemolysis such primary factors as complement activity and mechanical trauma and such secondary factors as erythrostasis and a suitable temperature (table 1). It is possible that other factors may also be involved in certain conditions, namely the p_H, the concentrations of such electrolytes as sodium

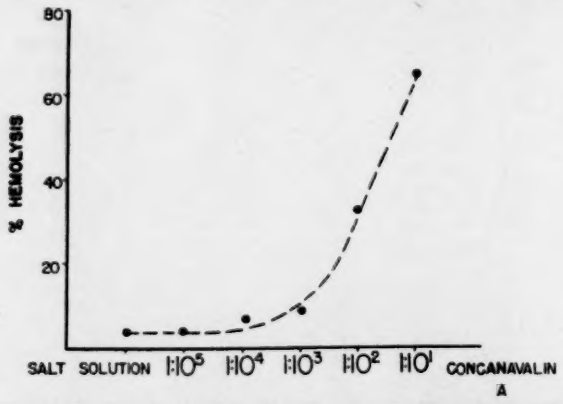

Fig. 13.—Hemolysis with concanavalin A and mechanical fragility (shaking three hours), showing the effect of various concentrations. Red cells agglutinated by concanavalin A were readily hemolyzed by the mechanical trauma of shaking with glass beads for three hours; the degree of hemolysis was dependent to a large extent on the concentration of concanavalin A used.

and potassium, the degree of glycolysis, certain physical factors and certain splenic activities other than those of stasis.

Our experiments indicated that silicic acid, immune hemolytic serum and concanavalin A all produced injury to the red cell, which could be demonstrated in various ways. When sensitized (agglutinated) by these substances the red cell became vulnerable to mechanical trauma, and with the first two substances to complement activity. A slight though definite increase in hypotonic fragility also became evident. In all the experiments, certain metabolic activities were apparent, as indicated by the definitely inhibitory effect of low temperatures and the greatly enhancing effect of incubator temperatures. In these in vitro experiments, erythrostasis of agglutinated red cells appeared to be of secondary importance as compared with the factors of mechanical trauma and complement activity. The nature of the injury to the erythrocyte produced by the various substances was studied by Reiner and Fischer,[9] who concluded that dehydration of the surface envelope

of the erythrocyte takes place, with the resultant changes in its colloidal structure. The thorn apple deformity seen by direct inspection is probably evidence of this.

The methods used for testing injury to the red cells in vitro probably have their counterparts in the pathologic processes of experimental and clinical hemolytic states. Thus, red cells sensitized by immune hemolysin and presumably first agglutinated become hemolyzed either by the mechanical trauma of passage through the circulation or by complement, a normal constituent of blood. It is probable that these two factors act together and are to some extent aided by stasis, since in our in vitro experiments stasis for a short time just prior to mechanical trauma appeared to enhance the effects of shaking. Red cells sensitized by a simple agglutinin, such as concanavalin A, may become hemolyzed in vivo owing to the combined activity of the factors of stasis and mechanical trauma.

Ham and Castle [8] have recently stressed erythrostasis as the basic factor underlying many, if not all, the hemolytic processes, both of experimental and of clinical origin. Chiefly on the basis of Knisely's work [11] they concluded that the normal spleen has two main functions, which are reproducible in the test tube:

TABLE 1.—*Hemolytic Mechanisms*

Simple (pure) hemolysin	→ Red blood cells	→ Hemolysis (complete) or Incomplete hemolysis (spherocytosis)		
Complex hemolysin / Immune hemolysin	→ Red blood cells	→ Agglutination (change in surface envelope) →	Complement activity / Mechanical trauma with and without stasis	→ Hemolysis (*a*) Complete (*b*) Incomplete (spherocytosis) → Stasis (spleen, etc.) → Hemolysis complete
Agglutinin: Autoagglutinin, Immune agglutinin, Concanavalin, Silicic acid	→ Red blood cells	→ "Sensitization" → Increased mechanical fragility → Hemolysis or Incomplete hemolysis		
Physical Agents: Heat, Cold, Mechanical trauma, etc.	→ Red blood cells	→ Hemolysis, complete or incomplete		

erythrostasis and erythroconcentration. They stated that unusual erythrostasis in the presence of normal red cells, which they conceived of as occurring in heart failure, "hypersplenic" anemia, favism, certain agglutination reactions, increased blood viscosity or the tendency to rouleau formation, is the cause of hemolytic anemia. The experimental hemolytic anemia which they produced by concanavalin A was interpreted as due to the extreme erythrostasis induced by the agglutinating effect of the chemical. The experimental hemolytic anemia of immune hemolytic serum, which Dameshek and Schwartz [2] stated was due to hemolysin activity, was interpreted by Ham and Castle as due to the action of the agglutinins present, with resultant "erythrostasis."

These conclusions are in several respects at variance with ours. There is in the first place very little evidence that unusual erythrostasis occurs in the various conditions listed. Furthermore, although the spleen is doubtless an organ of erythrostasis, it probably has other than purely "test tube" functions. Many of

11. Knisely, M. H.: Spleen Studies: I. Microscopic Observations of the Circulating System of Living Unstimulated Mammalian Spleens, Anat. Rec. **65**:23, 1936; II. Microscopic Observations of the Circulating System of Living Traumatized Spleens and of Dying Spleens, ibid. **65**:131, 1936.

its cells belong to the highly phagocytic reticuloendothelial system. According to Bergenhem and Fåhraeus,[12] the spleen contains in greatest concentration the physiologic lysin called lysolecithin, which may alter the thickness of the red cells. Other functions, such as the hormonal, have been listed by Singer, Miller and Dameshek.[13]

Regarding that group of hemolytic diseases in which spherocytosis is present and in which the hemolysis is said to be due to the effects of normal erythrostasis on abnormal red cells, Ham and Castle made no attempt to explain the reason for the presence of spherocytosis, even though in some cases a definite cause is present (sulfonamide drugs, arsine [AsH_3], etc.). It has been our contention that when a hemolytic substance produces incomplete hemolysis, spherocytosis results. The spherocyte may thus be said to be an indicator of hemolytic activity and appears after injury to the red cell by hypotonic solution of sodium chloride, saponin, lecithin, lysolecithin, immune hemolytic serum and even by such purely physical means as heat[13a] and mechanical trauma. According to this conception, the presence of spherocytosis in cases of hemolytic anemia, whether congenital or acquired, indicates not an abnormality in formation of the red cells but rather the presence of some sort of hemolytic agent—immunologic, chemical or physical—even though a hemolysin as such can only occasionally be demonstrated.

Our experiments with immune hemolytic serum in which various degrees of spherocytosis, increased hypotonic fragility and hemolytic anemia were produced seemed adequately explained on the basis of the hemolysin content of the serum. The actual hemolytic mechanism is, however, probably more complex than that of simple lysis. As pointed out previously, immune hemolytic serum, which is ordinarily considered to be simply a hemolysin, is in reality a complex material containing among other substances amboceptor, or sensitizer, which brings about agglutination and thus definite injury to the red cell. Attempts to differentiate clearly and to separate agglutinin from hemolysin have been for the most part unsuccessful, and for this and other reasons some immunologists have a "unitarian" concept of agglutination and hemolysis. Numerous experiments[13b] dating from the time of Bordet have shown that amboceptor differs from complement, which is the actual hemolyzing substance and which can act only on the already injured erythrocyte. In anemia due to concanavalin A, the mechanical trauma involved in the circulation of agglutinated masses of red cells may be of at least as much importance from the hemolytic standpoint as the factor of stasis. Thus our conception of hemolysis as an active process differs from that of Ham and Castle, who stress the more passive process of erythrostasis.

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12. Bergenhem, B., and Fåhraeus, R.: Ueber spontane Hämolysinbildung im Blut unter besonderer Berücksichtigung der Physiologie der Milz, Ztschr. f. d. ges. exper. Med. **97**:555, 1936.

13. Singer, K.; Miller, E., and Dameshek, W.: Hematological Changes Following Splenectomy in the Human with Particular Reference to Target Cells, Hemolytic Index, and Lysolecithin, Am. J. M. Sc. **202**:171, 1941.

13a. Isaacs, R.; Brock, B., and Minot, G. R.: Resistance of Immature Erythrocytes to Heat, J. Clin. Investigation **1**:425, 1925. Ham, T. H., and Chew, S. C.: Studies on Destruction of Red Blood Cells: III. Mechanism of Hemoglobinuria in Thermal Burns. Spherocytosis and Increased Osmotic Fragility of Erythrocytes, to be published.

13b. Lieberman, L. V., and Fenyvessy, B. V.: Ueber Serumhämolyse, Jahresb. f. Immunitätsforsch. u. exper. Therap. **7**:2, 1910. Ehrlich, P.: Experimentelle Untersuchungen über Immunität: I. über Ricin, Deutsche med. Wchnschr. **17**:976, 1891. von Baumgarten, P.: Die Osmologische Auffassung der Hämo- und Bakteriolyse, Biochem. Ztschr. **11**:21, 1908.

From the clinical standpoint, certain considerations are in order. Unusual erythrostasis without the presence of agglutinins (as in heart failure) has been stated to produce increased hypotonic fragility and hemolysis.[14] However, the increase in fragility is minimal, and the observed increase in fecal urobilinogen output is based not necessarily on erythrostasis but simply on an increased removal of red cells from the body. In polycythemia vera, in which erythrostasis, viscosity, decreased blood flow, etc., are maximal, there is no evidence of an increased hemolytic tendency; in fact, quite the reverse occurs.[14a] In multiple myeloma, in which the blood globulins are greatly increased, with resultant marked rouleau formation and actual pseudoagglutination, there is rarely any evidence of even a slight increase in hemolysis. In experiments on dogs with splenic vein thrombosis,[15] partial or complete, in which marked splenic stasis was present, there was no evidence of spherocytosis or increased hypotonic fragility. In fact, the red cells tended to become thinner (target cells) and more resistant to hypotonic solutions. In sickle cell anemia, Cooley's erythroblastic anemia, target cell anemia[16] and various types of Mediterranean anemia, there is usually increased hemolysis and yet the red cells are unusually resistant to hypotonic solutions of sodium chloride. All of these considerations tend to refute the conceptions of Ham and Castle regarding the importance of erythrostasis and agglutination in the development of increased hemolysis.

From the positive standpoint, furthermore, in certain cases acute hemolytic anemia is associated with the presence of hemolysins in the serum;[17] in paroxysmal (cold) hemoglobinuria an autohemolysin is present which appears to act directly on the red cells. Neither paroxysmal nocturnal hemoglobinuria[18] nor march hemoglobinuria[19] has been found to be concerned with the factors of agglutination or erythrostasis. The former condition appears to be concerned with the presence of sensitized red cells, which in the presence of complement become hemolyzed. In march hemoglobinuria, the sudden hemolysis is brought about by severe muscular exercise rather than by stasis. In cases of "symptomatic" hemolytic anemia,[4] in which the increased hemolysis is associated with some more fundamental condition, such as lymphatic leukemia, Hodgkin's disease and dermoid cyst, there is no evidence of stasis. Removal of a dermoid cyst in 1 of our cases resulted in complete cessation of the hemolytic process.

As previously stated, our conception of the various types of hemolytic syndromes remains an active one and is fundamentally concerned with the activity of hemol-

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14. Waller, J.: Cause of Increased Fragility of Erythrocytes in Congestive Heart Failure, Proc. Soc. Exper. Biol. & Med. **42**:64, 1939.

14a. Miller, E. B.; Singer, K., and Dameshek, W.: Use of the Daily Fecal Output of Urobilinogen and the Hemolytic Index in the Measurement of Hemolysis, Arch. Int. Med. **70**:722 (Nov.) 1942.

15. Miller, E. B.; Singer, K., and Dameshek, W.: Experimental Production of Target Cells by Splenectomy and Interference with Splenic Circulation, Proc. Soc. Exper. Biol. & Med. **49**:42 and 45, 1942.

16. Dameshek, W.: "Target Cell Anemia": An Erythroblastic Type of Cooley's Erythroblastic Anemia, Am. J. M. Sc. **200**:445, 1940.

17. Dameshek, W., and Schwartz, S. O.: Acute Hemolytic Anemia (Acquired Hemolytic Icterus, Acute Type), Medicine **19**:231, 1940.

18. Ham, T. H., and Dingle, J. H.: Studies in Destruction of Red Blood Cells: II. Chronic Hemolytic Anemia with Paroxysmal Nocturnal Hemoglobinuria; Certain Immunological Aspects of the Hemolytic Mechanism with Special Reference to Serum-Complement, J. Clin. Investigation **18**:657, 1939.

19. Gilligan, D. R., and Blumgart, H. L.: March Hemoglobinuria: Studies of the Clinical Characteristics, Blood Metabolism and Mechanism, with Observations on Three New Cases and Review of the Literature, Medicine **20**:341, 1941.

ysins. The word hemolysin may be utilized for any substance which injures the red cell, rendering it liable to hemolysis (tables 2 and 3). Included are: (*a*) pure or simple hemolysins (saponin, lecithin, lysolecithin, the Donath-Landsteiner hemolysin of paroxysmal cold hemoglobinuria, arsine and probably sulfanilamide, which causes changes in the hemoglobin structure of the red cell): (*b*) complex hemolysins (silicic acid, tannic acid, immune hemolysin and other ill defined hemolysins), and (*c*) agglutinins (isoagglutinins, autoagglutinins, panagglutinins and concanavalin A). In addition, there are probably hemolytic agents of more purely physical type—heat, cold, mechanical injury—which may directly

TABLE 2.—*Hemolytic Syndromes: Etiologic Factors*

Hemolysins	Agglutinins	Spleen	Inherited factors
Simple	Isoagglutinins	Passive (erythrostasis)	Sickle cell
Sulfanilamide	Transfusion reactions	Physical factors	Oval cell } Mediterranean anemia
Snake venom	Wrong type	Heat	Target cell }
Other chemicals, toxins	Subgroups	Cold	? Spherocyte
Complex—including immune hemolysis	Rh factor	Mechanical injury	
Known	Erythroblastosis foetalis	Congenital hemolytic jaundice	
Acute hemolytic anemia with hemolysinemia	Rh factor	Acquired spherocytosis	
Paroxysmal (cold) hemoglobinuria	Autoagglutinins	Various causes	
Possible	Acute hemolytic anemia	Active (abnormal)	
Acute hemolytic anemia without hemolysinemia	Sulfonamide drugs	Abnormal hemolysin production (hypersplenism)	
Congenital hemolytic jaundice	Virus pneumonia	Acute hemolytic anemia ?	
Symptomatic hemolytic anemia (leukemia, Hodgkin's disease, dermoid cirrhosis)		Congenital hemolytic jaundice crises ?	
Paroxysmal nocturnal hemoglobinuria			

TABLE 3.—*Development of Hemolytic Syndromes* *

Inherited factors: Target cell, Sickle cell, Spherocyte ?			
Hemolysins: Simple, Complex (may be of splenic origin)	→ Red blood cells	→ Injury to red blood cells	
		+	
		Stasis, Mechanical trauma, Complement activity, Splenic activity	→ Hemolysis; Incomplete hemolysis (spherocytosis)
Agglutinins: Simple, Complex			0.70 / 0.80 — 0.4 per cent sodium chloride
Physical factors			

* Hemolytic syndromes are due to red cell injury as a result of the activity of hemolysins, agglutinins, inherited factors and certain physical agents. The injured red cells are vulnerable to such factors as erythrostasis, mechanical trauma in the circulation, the activity of complement and splenic activity. As a result, either incomplete hemolysis (spherocytosis) or complete hemolysis results.

injure the exposed red cell. Certain hemolysins may be demonstrable in the blood; certain of them are demonstrable only by the effects they produce. Thus, spherocytosis without demonstrable hemolysins, red cells abnormally fragile to mechanical trauma and red cells abnormally susceptible to an acid p_H or to complement (paroxysmal nocturnal hemoglobinuria) may all indicate the effect of adsorption of hemolysin by the erythrocytes. The place of the spleen in this etiologic discussion is obscure. That it is a simple organ of erythrostasis and without other function is difficult to believe in view of the dramatic results which have attended splenectomy in certain of our cases of acquired acute anemia with or without hemolysinemia. In such cases the spleen is evidently a primary

organ in the production of hemolysin. In many cases of hemolytic anemia, however, the spleen is perhaps of only secondary importance. In certain cases of hemolytic anemia—sickle cell anemia, Mediterranean anemia of various grades of severity (Cooley's anemia, target cell anemia)—which are associated with an increased hypotonic resistance of the erythrocytes, the mechanisms of the increased hemolysis appear to be based on hereditary factors which are at present obscure.

We believe, therefore, that hemolytic syndromes are due to many different mechanisms rather than to some one etiologic factor (action of hemolysin, erythrostasis). Much work remains to be done in clarifying these mechanisms further and in applying knowledge of them to the clinical syndromes. In the present paper the injurious effects of pure and complex hemolysins and of agglutinin have been partially analyzed and the concept of erythrostasis criticized.

SUMMARY AND CONCLUSIONS

The effects on red cells of simple lysins, complex hemolysins and agglutinins were studied in relation to such factors as stasis, temperature, mechanical trauma and complement activity. The substances used were saponin (a simple lysin), colloidal silicic acid and immune hemolytic serum (complex hemolysins) and concanavalin A (a pure agglutinin).

Simple lysins act directly on the red cells, producing either complete hemolysis or spherocytosis—incomplete hemolysis. Complex hemolysins produce sensitization (actually agglutination) by means of amboceptor and then hemolysis by means of (*a*) complement activity or (*b*) mechanical trauma. A pure agglutinin produces agglutination; hemolysis may then be produced by mechanical trauma (shaking with glass beads). The factor of erythrostasis in our experiments seemed minimal.

We believe that hemolysis is an active process due to red cell injury by a variety of agents, such as: pure hemolysins, complex hemolysins or agglutinins. Red cell injury may be measured not only by an increase in hypotonic fragility (present only with spherocytosis) but by other means, such as the mechanical fragility, the reaction to an acid p_H and the reaction to complement. Erythrostasis, a passive phenomenon, is probably of only minor importance in the hemolytic processes. In polycythemia vera and splenic vein thrombosis, in which erythrostasis is marked, and in multiple myeloma, with increased rouleau formation and pseudo-agglutination, increased hemolysis is not present.

We believe that spherocytosis indicates incomplete hemolysis by means of the activity of some hemolytic agent, the presence of which may or may not be readily discernible. The spherocyte is vulnerable to stasis and may become completely hemolyzed by this means. Thus, stasis may be of only secondary importance to the activities of hemolysin, agglutinin and other factors.

The place of the spleen is still obscure. We believe, however, that it is probably more than a simple organ of stasis and may have an active hemolytic function, particularly in certain cases of acquired hemolytic anemia.

Hemolytic processes are probably due to various causes, among them being the activity of hemolysins, both simple and complex, and of agglutinins; certain hereditary injuries to the red cells and certain splenic dysfunctions. It is impossible to explain hemolysis on the basis of a single factor, such as erythrostasis (Ham and Castle) or the activity of hemolysins (Dameshek and Schwartz). If by hemolysin is meant any substance causing injury to the red cells, the latter theory seems more probable.

113 Bay State Road.

CLINICAL MANIFESTATIONS OF WEIL'S DISEASE WITH PARTICULAR REFERENCE TO MENINGITIS

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AND
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DETROIT

Before 1935 only 11 cases of Weil's disease had been reported from the United States.[1] Since that time additional cases have been reported with increasing rapidity.[2] Several excellent summaries [3] of the clinical manifestations of the disease have also appeared in the American and foreign literature. Nevertheless it is still not widely appreciated in America that this malady may occur in a meningitic form and that jaundice is not a necessary concomitant.

HISTORY AND INCIDENCE OF MENINGITIS IN WEIL'S DISEASE

What would appear to be the first recorded case of meningitis in Weil's disease was reported by Laubry and Parvu,[4] of Paris, France, in October 1910. These authors described 3 atypical cases of lymphocytic meningitis; 1 of the patients had jaundice and a clinical course which simulated that of Weil's disease. One week later Gullain and Richet [5] described, and illustrated with 4 case reports, a distinct clinical syndrome of jaundice and meningitis, which in retrospect was probably Weil's disease. It remained, however, for Costa and Troisier,[6] in 1916, to demonstrate that Leptospira icterohaemorrhagiae was responsible for the condition and that the meningeal form could occur without jaundice.

As European physicians, particularly those in the Netherlands, have become more conscious of the disease and its variations, an increasing number of cases of the nonicteric and meningeal form have been reported. A fair proportion of the cases without jaundice have been characterized by the meningeal syndrome.

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5. Gullain, G., and Richet, C.: Étude sûr une maladie infectieuse caracterisée par de l'ictère et un syndrome méningée, Bull. et mém. Soc. méd. d. hôp. de Paris **30**:289-299 (Oct. 28) 1910.

6. Costa, S., and Troisier, J.: Réactions méningées dans la spirochetose ictéro-hemorragique: Virulence du liquide cephalorachiden, Bull. et mém. Soc. méd. d. hôp. de Paris **40**:1802-1806 (Nov. 10) 1916. Costa, S., and Troisier, J.: Méningite avec subictère dans la spirochétose ictérhémorragique, ibid. **40**:1928-1931 (Nov. 24) 1916.

Between 1924 and 1939 Walch-Sorgdrager,[3] of Amsterdam, confirmed the diagnosis of 327 cases by either bacteriologic or serologic means. Of these, 129 cases were without jaundice. Twenty of the nonjaundiced patients presented the clinical picture of serous meningitis. As his study progressed, the incidence of the meningitic form increased, cases of that type comprising about one third of the cases without jaundice reported during the last two years. In about 10 per cent of the 248 cases of Weil's disease reported from Great Britain prior to 1939 there was clinical and laboratory evidence of meningitis.[7] In the American literature cases of Weil's disease with meningitis and jaundice have been reported by Goldberg and Davens [8] and Bloom and Walker.[9]

Within the past year and a half we have observed 13 cases of Weil's disease which reemphasized the frequency of meningeal involvement in this malady. In 2 of these cases there was both clinical and laboratory evidence of meningitis; in 7

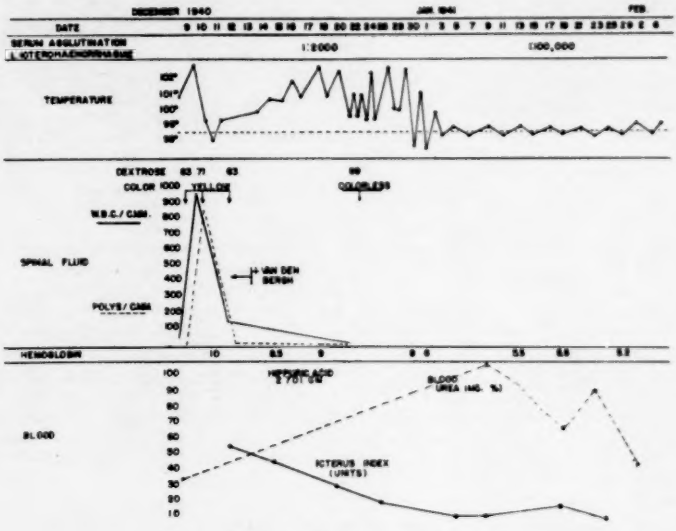

Chart 1.—Data in case 1.

there was an abnormal cellular reaction in the cerebrospinal fluid without clinical signs of meningeal irritation, and in 1 instance meningismus was present without pleocytosis of the cerebrospinal fluid. Lumbar puncture was not performed in 3 of the cases. All the patients presented clinical evidence of hepatitis during some phase of the illness.

REPORT OF CASES WITH MENINGITIS

Case 1.—J. E., a Negro poultry worker aged 56, was admitted to the City of Detroit Receiving Hospital during a generalized epileptiform convulsion on Dec. 9, 1940. The history, obtained from his wife, revealed that he was well until December 3, when he began to complain of generalized muscular aches. On December 5 he suffered a chill, and on

7. Davidson, L. S. P., and Smith, J.: Weil's Disease in the North-East of Scotland: An Account of One Hundred and Four Cases, Brit. M. J. **2**:753-757 (Oct. 14) 1939.

8. Goldberg, H. P., and Davens, E. D.: Weil's Disease: Case Presentation, Bull. Johns Hopkins Hosp. **68**:112-113 (Jan.) 1941.

9. Bloom, N., and Walker, H.: Spirochetal Jaundice (Weil's Disease), Virginia M. Monthly **68**:192-200 (April) 1941.

the following morning a cough productive of bloody sputum was present. Shortly thereafter he became nauseated and vomited repeatedly. Convulsions commenced the day before admission. The past history was negative save that as a youth he had had a penile lesion.

Examination revealed an unconscious, dehydrated Negro man with icterus of the scleras and injection of the conjunctivas. The pupils reacted to light, and the optic fundi were normal. There were no extraocular or cranial nerve palsies. Old dried blood was present in both nares, and the lips and the tongue were dry. The neck was markedly rigid, and both Kernig and Brudzinski signs were present. The lung fields were resonant to percussion, and a few scattered coarse rales were heard. An edge of the liver, soft but sharp, and tender, was palpated 5 cm. below the right costal margin. The spleen was not palpated. There was no lymphadenopathy. No paralysis was noted. The deep reflexes were equal and active, and no pathologic reflexes were elicited.

By lumbar puncture, a clear, golden yellow cerebrospinal fluid was obtained, which was under normal pressure. This contained 52 white cells per cubic millimeter, of which 50 per cent were polymorphonuclear (chart 1). Since the patient was in contact with rats at his work in a poultry house and because of the presence of jaundice, hepatomegaly, severe pain of muscles, hemorrhagic manifestations and meningeal involvement, a clinical diagnosis of Weil's disease was made. The cellular reaction in the cerebrospinal fluid, as may be seen in chart 1, reached its peak on December 10, when 990 white cells per cubic millimeter were

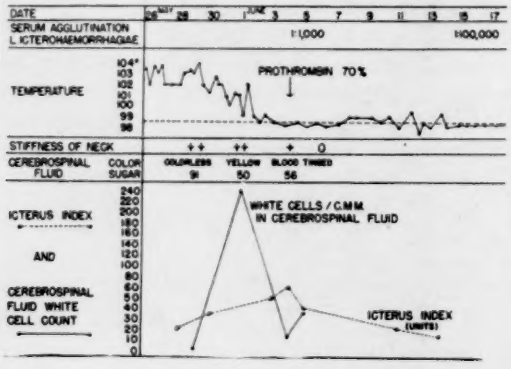

Chart 2.—Data in case 2. The patient presented meningismus with pleocytosis of the cerebrospinal fluid.

present. Ninety per cent were polymorphonuclear. The fluid was still yellow on December 12, and a qualitative van den Bergh test performed on this specimen became weakly positive at the end of six minutes. The meningeal signs and symptoms cleared in several days, and the cerebrospinal fluid quickly became normal. Kahn and Kline tests of the patient's blood serum were positive but those of the cerebrospinal fluid were negative. The subsequent course of illness in the hospital was that of low grade hepatitis with progressive hypochromic, microcytic anemia. Specimens of serum obtained on Dec. 19, 1940 and Jan. 18, 1941, diluted 1:2,000 and 1:100,000 respectively, agglutinated L. icterohaemorrhagiae.[10] He was discharged improved Feb. 10, 1941.

Case 2.—L. D., an unemployed Negro youth aged 18, was admitted to the City of Detroit Receiving Hospital on May 26, 1942. His health had been good until the morning of May 25, when headache, nausea and vomiting developed. He was awakened by a true chill the following morning and was brought to the hospital a few hours later.

Examination on admission revealed an acutely ill Negro youth with a temperature of 103 F. The conjunctivas were injected, and the scleras were not icteric. The heart and the lungs were normal. There was considerable tenderness, with voluntary splinting of the abdominal wall, in the right upper quadrant. No abdominal masses were palpated. Two large infected

10. The agglutinations were reported to us by Dr. Carl L. Larson, of the National Institute of Health, Bethesda, Md., Dr. K. F. Meyer, of the Hooper Foundation of the University of California, San Francisco, and Dr. Joseph Kasper and Mrs. C. R. Broom, of the Detroit Board of Health.

blisters were present on the left hand. Both the epitrochlear and the axillary lymph nodes on the left were enlarged and tender.

Bacteremia from the infection of the hand was considered, but the leukocyte count was low and blood cultures showed no growth. On May 29 slight jaundice was noted. The neck was stiff, and Kernig and Brudzinski signs were present. The possibility of complicating abscesses of the brain and the liver was considered, and a lumbar puncture was performed. The cerebrospinal fluid was completely normal. On June 1 the urine revealed albumin as well as occasional white cells and 100 red cells per high power field. By a second lumbar puncture, a clear yellow cerebrospinal fluid was obtained, which contained 242 white cells per cubic millimeter. Eighty per cent were lymphocytes (chart 2). A pellicle appeared after the spinal fluid had stood a few hours. Since repeated blood cultures were negative, and the infection of the hand had subsided almost completely, it became evident, at this point, that the jaundice, meningismus, pleocytosis of the cerebrospinal fluid, conjunctival injection and microscopic hematuria were all due to Weil's disease rather than to septicemia from the manual focus of infection. The patient when questioned carefully denied any contact with rats but admitted that he not uncommonly visited poultry houses and stood in the water while watching the employees at work.

The temperature remained near 103 F. during the first four days of hospitalization and then, during the next four days, fell to normal by lysis. The icterus index reached a peak of 60 units on June 4 and then gradually fell to 16 units before discharge. Results of the remaining laboratory studies are shown in table 1. After the temperature reached normal on June 2, the rigidity of the neck disappeared, and the patient rapidly became asymptomatic. Specimens of blood serum secured on June 5 and June 16 agglutinated L. icterohaemorrhagiae in dilutions of 1 : 1,000 and 1 : 100,000 respectively. The patient was discharged well on June 18.

REPORT OF CASES WITH CELLULAR CHANGES IN THE CEREBROSPINAL FLUID BUT WITHOUT MENINGISMUS

Case 3.—T. J., a Negro man aged 39, was admitted to the City of Detroit Receiving Hospital Aug. 25, 1941. He had been well until August 19, when severe headache, marked anorexia, nausea and vomiting developed. Fever without chills commenced the next day. Urinary frequency and dysuria appeared on August 21, with the urine becoming a deep golden brown. He stated that his home was so infested with rats that it was frequently necessary for him to discard food because it was contaminated with their excreta.

Examination revealed a well developed and well nourished Negro man, who appeared older than his stated age and moderately ill. The conjunctivas were markedly injected, and the scleras were jaundiced. There was no stiffness of the neck. Kernig and Brudzinski signs were absent. The spleen and the liver were not palpated. There was moderate generalized lymphadenopathy. The course of his illness in the hospital aside from a temperature of 100 F. on the day of admission was afebrile. The initial icterus index of 64 units fell to 21 before discharge. By lumbar puncture on August 29, a clear, pale yellow cerebrospinal fluid was obtained, which showed a trace of globulin. It became colorless on standing five hours. There were 14 white cells per cubic millimeter. Eighty-five per cent were lymphocytes (table 2). The Kline test was negative. A 1 : 100,000 dilution of the patient's serum obtained on August 27 agglutinated L. icterohaemorrhagiae. He was discharged, much improved, on September 12.

Case 4.—A. J., a white slaughterhouse worker aged 52, was admitted to the City of Detroit Receiving Hospital on Nov. 24, 1941. He had been well until November 17, when he experienced chilly sensations, fever, weakness and severe aching pains in the muscles of his arms and legs. He became jaundiced several days before admission.

Examination revealed a moderately ill white man with Kussmaul respiration and deep orange jaundice. The nose contained dried blood. The neck was not stiff, and Kernig and Brudzinski signs were absent. The heart and the lungs were normal aside from frequent extrasystoles. A sharp, firm edge of the liver was palpated 8 cm. below the right costal margin. The spleen and the kidneys were not palpable. On November 29 a generalized erythematous, morbilliform eruption suddenly appeared on the trunk and extremities. It faded rapidly and had disappeared by December 4.

The icterus index reached a peak of 300 units on November 29 and then fell rapidy to 50 units by December 4. During this same period the urea fell from 312 to 38 mg. per hundred cubic centimeters of blood. By lumbar puncture on November 29, a clear, deep golden yellow cerebrospinal fluid was obtained, which contained 0.55 mg. of bilirubin per hundred cubic centimeters and gave an immediate direct but weak van den Bergh reaction. Twelve lymphocytes per cubic millimeter of cerebrospinal fluid were present (table 2). The temperature ranged between 98 F. and 102 F. until December 8, after which the patient was

afebrile. Specimens of serum obtained on December 8 and 23, diluted 1:1,000 and 1:100,000 respectively, agglutinated L. icterohaemorrhagiae. The patient was discharged improved on Jan. 28, 1942.

CASE 5.—E. H., a white junk collecter aged 47, was admitted to the City of Detroit Receiving Hospital on Dec. 6, 1941. He had been well until November 30, when chilly sensations and severe aching pains in the legs, arms and back developed. He also became nauseated and vomited repeatedly. Before admission his urine became a dark amber color but the appearance of his stools remained normal.

Examination on admission revealed a thin, jaundiced white man, who did not appear acutely ill. The scleras were icteric, and conjunctival injection was present bilaterally. The neck was not stiff, and Kernig and Brudzinski signs were not present. A soft but sharp, nontender liver edge was palpated 3 cm. below the right costal margin. The spleen was not felt. The remainder of the physical examination yielded negative results.

The temperature reached 100 F. during the first three days of hospitalization but was normal thereafter. The urea content of 232 mg. per hundred cubic centimeters of blood found on December 8 fell to 60 in the next five days. The icterus index decreased from 94 to 40 units between December 9 and 20. By lumbar puncture on December 9, a clear golden yellow fluid was obtained. It contained 0.56 mg. of bilirubin per hundred cubic centimeters. There were 93 white cells per cubic millimeter of fluid. Eighty-two per cent of these were lymphocytes (table 2). The van den Bergh reaction of the cerebrospinal fluid was direct, immediate and weak. Dark field examination of the patient's blood on December 6 failed to reveal any leptospiras. Specimens of blood serum obtained on Dec. 23, 1941 and Jan. 6, 1942, diluted 1:10,000 and 1:100,000 respectively, agglutinated L. icterohaemorrhagiae. He was discharged well Jan. 17, 1942.

CASE 6.—E. Tr., a white man aged 33, was admitted to the City of Detroit Receiving Hospital Dec. 8, 1941. He had been well until the morning of December 1, when, while at work as a syrup mixer in a soft drink factory, he began to have aching pains in the muscles and joints of the extremities. He was confined to bed because of extreme weakness, and on December 5 epistaxis developed and his temperature rose to 103 F. Chilliness, anorexia, nausea and vomiting soon followed. The urine became amber in color on December 6. Jaundice was detected the day before admission.

Examination revealed a well developed and not acutely ill white man deeply bronzed from jaundice. The scleras were icteric and the conjunctivas injected, and there were several subconjunctival hemorrhages. The pharynx was slightly injected, and a few shotty cervical lymph nodes were palpable. The neck was not stiff, although there was some discomfort on flexion. A firm, sharp edge of the liver was palpated 1 cm. below the right costal margin. The spleen was not palpated. Small brownish purpuric spots were present in the skin over the ankles and tibias. The muscles of both calves were tender. Kernig and Brudzinski signs were not obtained.

Characteristic leptospiras were found on dark field examination of the patient's blood on December 8, and the serum van den Bergh reaction was direct, immediate and strong. The icterus index, which was 109 units on admission, fell to 25 in the course of one week. By lumbar puncture on December 9, a clear, light golden yellow fluid was obtained, which contained 0.33 mg. of bilirubin per hundred cubic centimeters of cerebrospinal fluid. There were 94 white cells per cubic millimeter, and of these 6 per cent were polymorphonuclear (table 2). The van den Bergh reaction of the cerebrospinal fluid was direct, immediate and weak. A 1:100,000 dilution of blood serum, obtained on December 23, agglutinated L. icterohaemorrhagiae. After a mild and afebrile hospital course, he was discharged well on December 23.

CASE 7.—E. Tu., a Negro poultry worker aged 40, was admitted to the City of Detroit Receiving Hospital on Dec. 16, 1941. He had been well until December 12, at which time he became weak and chilly and noted that his teeth were sore. The next day aching pains appeared in his legs. Shortly before admission to the hospital he noticed that his urine was dark amber in color. He did not inspect his stools.

Examination on admission revealed a drowsy, dehydrated Negro man, who appeared acutely ill. The conjunctivas were injected, and the scleras were deeply jaundiced. There was no stiffness of the neck, and Kernig and Brudzinski signs were absent. Neither the liver nor the spleen was palpated. Slight tenderness of a calf was present.

He experienced severe shaking chills on December 16, the day of admission, and on December 17, but thereafter the temperature did not exceed 101 F. It was normal after Jan. 3, 1942. The icterus index, which was 250 units on admission, fell rapidly to 55 units on December 24. By lumbar puncture on December 17, a clear, pale lemon yellow fluid was obtained, which contained 81 white cells per cubic millimeter. Seventy-six per cent were lymphocytes (table 2). The van der Bergh reaction of the cerebrospinal fluid became weakly

positive at the end of eight minutes. Dark field examination of the patient's blood on the day of admission failed to reveal any leptospiras. A 1:100,000 dilution of a specimen of blood serum obtained Jan. 6, 1942 agglutinated L. icterohaemorrhagiae. He was discharged, much improved, January 14.

CASE 8.—H. G., a white farmer aged 28, was admitted to the City of Detroit Receiving Hospital July 27, 1942. He had been in good health until the morning of July 17, when he experienced chilly sensations, became nauseated and commenced to vomit. These symptoms persisted, and he became progressively weaker until July 21, when severe aching pains developed in the extremities, particularly in the calves of the legs. At that time he noted that his urine was dark and his stools light, but jaundice was not detected until July 27, the day of admission. He stated that rats were present on the farm where he was employed, but he was not aware of any close contact with them.

Examination on admission revealed an acutely ill jaundiced white man with a temperature of 102 F. The conjunctivas and the pharynx were markedly injected. The neck was not stiff, but some tenderness was present on flexion. Kernig and Brudzinski signs were absent. The heart and the lungs were normal to physical examination. The blood pressure was 80 systolic and 55 diastolic. A firm, sharp edge of the liver was palpated 5 cm. below the right

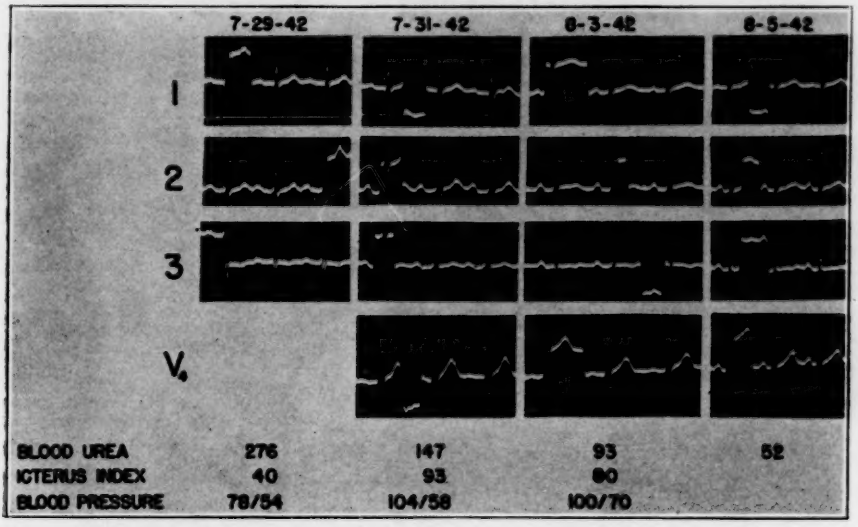

Chart 3.—Electrocardiograms in case 8, showing delayed auriculoventricular conduction in Weil's disease.

costal margin. The spleen was not palpated. The muscles of the extremities were very tender. Because of the characteristic history and the findings from physical examination a tentative diagnosis of Weil's disease was made.

Persistent hiccups and intense pruritus appeared on July 28. During the next twenty-four hours a moderate oliguria developed with the formation of only 6 ounces (170 cc.) of urine. At the end of this period the urea had reached 276 mg. per hundred cubic centimeters of blood (chart 3). Since necropsy studies in cases of Weil's disease [2b] have revealed degeneration of the adrenal cortex, the patient's hypotension and oliguria were treated with desoxycorticosterone acetate, in addition to transfusion of a half liter of blood and repeated intravenous administration of 5 per cent dextrose in saline solution. The next day, July 30, the blood pressure reached 96 systolic and 60 diastolic, and the blood urea commenced to fall (chart 3). The temperature gradually decreased, reaching normal on July 30. It remained normal until August 5; than it rose to 101 F. and continued at about this level for five days, after which it became and remained normal. By lumbar puncture on July 31, a clear, light yellow cerebrospinal fluid, was obtained, which contained 81 white cells per cubic millimeter. Eighty per cent were polymorphonuclear. The van den Bergh reaction of this fluid was direct, immediate and weak (table 2). An electrocardiogram taken on July 29 was normal save for considerably delayed auriculoventricular conduction. This was still

present on August 3, but two days later, had reverted to normal limits (chart 3). With the fall of the urea to normal, the hiccups disappeared and the remainder of the course in the hospital was uneventful. A specimen of blood serum secured August 20, diluted 1:1,000,000, agglutinated L. icterohaemorrhagiae. He was discharged much improved August 29.

CASE 9.—G. H., a Negro fish cutter aged 39, was admitted to the City of Detroit Receiving Hospital on Aug. 8, 1942. He had been taken ill suddenly on the evening of August 6 with a chill, a sharp, stabbing pain in the left upper quadrant of the abdomen, headache, and aching pains in the muscles of the extremities. He experienced a second chill the next day and a third shortly before admission, August 8. At that time he became nauseated and commenced to vomit. Pain and burning on urination were experienced at the beginning of his illness, and the day before admission he noted that his urine was dark orange.

He had had repeated admissions to this hospital dating back as far as 1922. He stated that during recent months his activity had been limited because of syphilitic heart disease, for which he had been receiving treatment.

Examination on admission revealed a slight jaundiced Negro man, who was acutely ill. Both pupils reacted to light and in accommodation. The conjunctivas and the pharynx were slightly injected. No stiffness of the neck was present. Subcrepitant inspiratory rales were heard over the lower thirds of both lung fields posteriorly. The apical impulse was palpated 11 cm. to the left of the midsternal line in the fifth interspace. The rate and the rhythm were regular, and systolic and diastolic blowing murmurs were heard over the entire precordium. The murmurs were loudest in the second right interspace adjacent to the sternum. Systolic blood pressure was 140; diastolic, 50. The abdomen was soft, with moderate tenderness in the left upper quadrant. Neither the liver nor the spleen was palpated. Moderate tenderness of the calves was present. Kernig and Brudzinski signs were absent. In view of the patient's occupation and rather characteristic history Weil's disease seemed the most likely explanation for his jaundice. He also had slight heart failure due to syphilitic aortic insufficiency.

By lumber puncture on August 13, a pale yellow cerebrospinal fluid was obtained on which the van den Bergh reaction was direct, immediate and weak. This contained 40 white cells per cubic millimeter, of which 90 per cent were polymorphonuclear (table 2). Positive Kline reactions were obtained on both the blood serum and the cerebrospinal fluid. The colloidal gold test performed on the latter gave a paretic type of curve. The patient quickly improved after admission to the hospital and received no specific treatment for his Weil's disease. A specimen of blood serum obtained August 20 agglutinated L. icterohaemorrhagiae when diluted 1:1,000,000. His hospital coarse was quite uneventful, and he was discharged improved September 13.

REPORT OF A CASE WITH MENINGISMUS BUT WITHOUT PLEOCYTOSIS OF THE CEREBROSPINAL FLUID

CASE 10.—L. G., a Negro automobile washer aged 39, was admitted to the City of Detroit Receiving Hospital on Nov. 29, 1941. He had been well except for a slight cold until November 27, when he noticed weakness, anorexia and severe aching pain in the back and the extremities.

Examination on admission revealed an acutely ill, drowsy, dehydrated Negro man with sunken eyeballs. Because of the presence of marked rigidity of the neck, as well as Kernig and Brudzinski signs, a tentative diagnosis of tuberculous meningitis was made. Lumbar puncture, however, revealed a completely normal cerebrospinal fluid. Weil's disease was considered at this time but was not definitely diagnosed until the appearance of slight icterus of the scleras, on December 1, two days after admission. Auricular fibrillation commenced on the morning of December 2. That afternoon two physicians independently demonstrated typical leptospiras on dark field examination of the patient's blood. The urea reached a peak of 420 mg. per hundred cubic centimeters of blood on December 3, at which time a pericardial friction rub was heard in the fourth left interspace adjacent to the sternum. Serial electrocardiograms (chart 4) confirmed the presence of auricular fibrillation and revealed elevation of the ST segments in leads II and III, characteristic of pericarditis. The latter was believed to be of fibrinous type, the result of uremia.

Both friction rub and auricular fibrillation had disappeared by December 4. In the course of one week the urea fell to 34 mg. per hundred cubic centimeters of blood. During this period the jaundice became deeper, and epistaxis, bleeding from the gums and hemorrhagic herpes appeared. The icterus index, which reached 150 units on December 8, gradually declined to 19 units on December 29.

The blood pressure bordered on shock levels (chart 4) until a transfusion of half a liter of convalescent blood from the patient in case 4 was given on December 8. The temper-

ature fluctuated between normal and 103 F. until December 15, nineteen days after the onset of his illness. It did not rise above 100 F. thereafter and gradually leveled off to normal. The initial hemoglobin of 11.5 Gm. per hundred cubic centimeters of blood slowly fell to 6 Gm. and then increased slowly in response to iron therapy (chart 4). By a second lumbar puncture, December 12, a clear, yellow fluid was obtained, which contained 4 white cells per cubic millimeter and 0.6 mg. of bilirubin per hundred cubic centimeters. The van den Bergh reaction of the cerebrospinal fluid was direct and immediate but weak (table 2). A 1:100,000 dilution of blood serum obtained December 23 agglutinated L. icterohaemorrhagiae. The patient was discharged much improved Jan. 26, 1942.

REPORT OF REMAINING CASES

Case 11.—V. C., a Mexican poultry worker aged 46, was admitted to the City of Detroit Receiving Hospital on Feb. 1, 1941. He had considered himself well until January 26, when

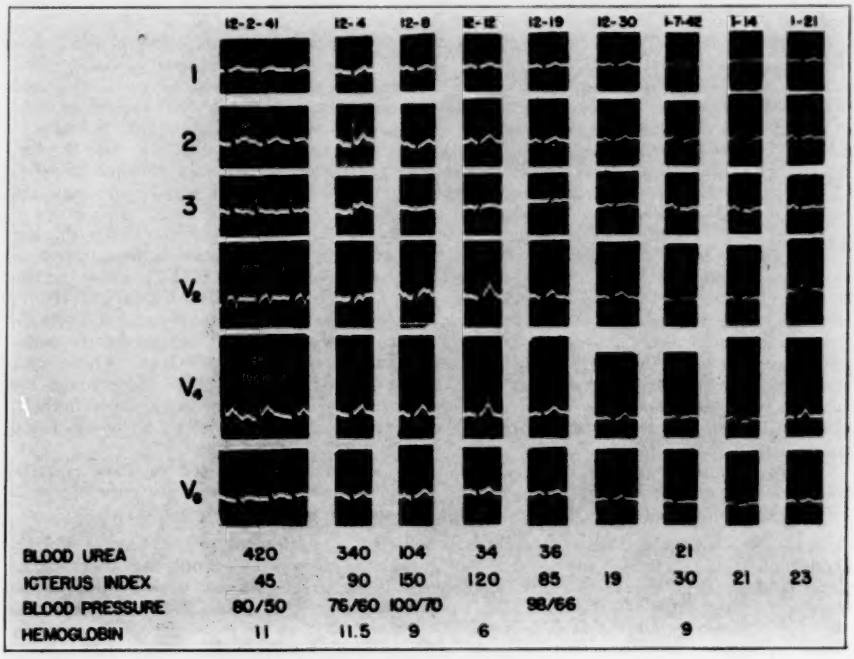

Chart 4.—Electrocardiograms in case 10.

severe aching pains developed in his legs, shoulders and lumbar region. Later the same day he felt feverish and vomited repeatedly. On January 30 his stools became light and his urine dark, and his skin assumed a yellow color.

Examination on admission revealed a deeply jaundiced, acutely ill Mexican man. His face and eyelids were puffy, and his scleras were a deep yellow. The neck was not stiff, and Kernig and Brudzinski signs were absent. There was a dark red maculopapular eruption over the trunk, with a purpuric eruption over the legs. Capillary resistance as determined by the Rumpel-Leede test was markedly decreased. The heart was not enlarged, and a systolic murmur was present at the apex. The abdomen was distended with fluid, and a sharp edge of the liver was ballotable 4 cm. below the right costal margin. The spleen and the kidneys were not palpated.

The temperature fluctuated between 100 F. and 104 F. during the first week of hospitalization. It fluctuated between 99 F. and 102 F. during the remainder of February, leveling off to normal early in March, five weeks after the onset of the illness. At admission the icterus

index was 120 units; it gradually fell, reaching 10 units on March 7. The serum albumin, which was 2.5 Gm. per hundred cubic centimeters on February 8, increased to 4.4 Gm. by February 17. Inasmuch as albuminuria was slight, impaired synthesis of serum proteins, the result of damage of the liver, seemed the most likely cause. Concomitant with this increase of serum proteins the edema decreased markedly, the ascites disappeared, and the patient's weight fell from 182 to 165 pounds (from 82.5 to 74.5 Kg.). The prothrombin, which was reduced to 55 per cent, returned to normal after administration of synkamin (4-amino-2-methyl-1-naphthol hydrochloride), a synthetic substance with vitamin K activity. Specimens of serum obtained on February 12 and 27, diluted 1:10,000 and 1:100,000 respectively, agglutinated L. icterohaemorrhagiae. The patient was discharged much improved March 10.

Case 12.—O. F., a white brewery worker aged 64, was admitted to the City of Detroit Receiving Hospital on Feb. 18, 1941. He had been in good health until February 4, when severe aching pains developed in the muscles of his legs. On February 15, while at work, he became acutely ill with nausea, vomiting, diarrhea, rectal incontinence and hallucinations. That afternoon he experienced two chills. The next morning his urine was dark, but jaundice was not noticed until the day before admission.

Examination revealed an acutely ill, semiconscious aged white man. The jaundice was deep, having somewhat of an orange hue. His lips were dry, and the tongue was dry and heavily coated. The neck was not stiff, and there was no lymphadenopathy. Kernig and Brudzinski signs were not present. The lungs were resonant, and a few inspiratory subcrepitant rales were heard at both bases posteriorly. The heart was slightly enlarged to percussion, and no murmurs were heard. The systolic blood pressure was 132; the diastolic, 105. The abdomen was distended with gas. The spleen, the liver and the kidneys were not palpated. A few small ecchymoses were present over both legs. The icterus index was 70 units, and the urea, 188 mg. per hundred cubic centimeters of blood. The urine contained albumin (4+ and bile 2+) in addition to 35 white cells and 100 red cells per high power field (table 1). Treatment consisted of intravenous injection of dextrose in saline solution, administration of synkamin and transfusion of a half liter of blood from the patient in case 11, whose serum, diluted 1:10,000, agglutinated L. icterohaemorrhagiae. The temperature, which was 100 F. on admission, steadily rose until it reached 104 F. at the time of death on February 21.

At autopsy the heart was found to weigh 450 Gm. The epicardial surface and the endocardial surface over the chordae tendinae showed a few minute hemorrhages. There were numerous widely distributed pinpoint hemorrhages on the surfaces of both kidneys and the small bowel, particularly the ileum. In sections stained by a silver impregnation technic, occasional leptospiras were found in the cellular detritus in the renal tubules. None was found in the liver.

Microscopic study of the nervous system disclosed multiple localized capillary ectasias, mostly in one subcortical region, but also involving the deepest portion of the cortex. Small lymphocytic infiltrations were present in the adventitia of the subependymal vessels.[11]

Case 13.—F. H., a Negro odd job man aged 51, was admitted to the City of Detroit Receiving Hospital June 8, 1941. He had considered himself well until the afternoon of June 2, when he had several chills, followed by headache and intense aching pains in the extremities, particularly in the legs. The next day his eyes were yellow and marked anorexia without vomiting or abdominal pain appeared. These symptoms persisted until June 8, when, after a nosebleed, he was hospitalized. He was not aware of any close contact with rats or their excreta.

The patient was a well developed and well nourished Negro man, who did not appear acutely ill. His neck was not stiff, and Kernig and Brudzinski signs were absent. The remainder of the examination gave negative results aside from marked jaundice of the scleras and a firm, sharp, slightly tender edge of the liver, which was palpable 1.5 cm. below the right costal margin. Kline and Kahn tests of the patient's serum were positive. Blood serum obtained on June 9 and August 21, diluted 1:1,000 and 1:100,000 respectively, agglutinated L. icterohaemorrhagiae. By lumbar puncture two weeks after admission, a completely normal cerebrospinal fluid was obtained. On admission the urea was 204 mg. per hundred cubic centimeters of blood and the icterus index 176 units. They gradually fell to normal. A finely papular pruritic eruption appeared over the trunk on June 18 and faded within a few days. The entire course of his illness in the hospital was mild and practically afebrile. The patient was discharged, much improved, on July 10.

11. This pathologic report is included with the permission of Dr. Osborne A. Brines, pathologist at the City of Detroit Receiving Hospital and associate professor of pathology at the Wayne University College of Medicine.

TABLE 1.—*Laboratory Studies in Weil's Disease*

Patient	J. E.	L. D.	T. J.	A. J.	E. H.	E. Tr.	E. Tu.	H. G.	G. H.	L. G.	V. C.	O. F.	F. H.
Case	1	2	3	4	5	6	7	8	9	10	11	12	13
Urine													
Albumin (range)	0-2+	0-1+	0-Tr.	Sl.Tr.-3+	Sl.Tr.-2+	2+-Tr.	Tr.-1+	0-3+	0-2+	4+-Sl.Tr.	0-2+	4+	0-Tr.
Red cells (range per high power field)	25-0	0-100	4-0	Occ.-0	0	0	0-Occ.	0-2	0-3	Many-0	0	100	0
White cells (range per high power field)	0-20	0-3	0-5	15-0	20-0	18-3	0-10	0-120	0-8	80-0	0-20	35	0-12
Urobilinogen (highest concentration)	1:150	1:50	1:300	1:170	1:10	1:20	1:10	Trace	1:90	1:100	1:90	—	1:150
Blood													
Agglutinins (highest titer)	1:100,000	1:100,000	1:100,000	1:100,000	1:100,000	1:100,000	1:100,000	1:1,000,000	1:1,000,000	1:100,000	1:100,000	—	1:100,000
Urea (highest value, mg. per 100 cc.)	108	35	39	312	232	52	90	276	59	420	64	188	204
White cells (highest count per cu. mm.)	22,850	9,500	28,300	25,650	21,000	19,200	16,050	20,900	12,000	18,250	27,550	19,100	19,100
Polymorphonuclears (highest %)	81	93	88	94	86	83	93	95	76	95	88	93	93
Hemoglobin (Gm. per 100 cc.)													
Initial	10	12	13	12	11.5	13	9.5	11	14	11.5	10	16	12
Lowest	5.2	9	10	5.5	10.5	12	8.5	11	12	6	8.5	14.5	8
Prothrombin (lowest %)	76	70	57	81	60	77	—	60	59	55	55	66	80
Icterus index (highest value, units)	54	60	64	300	94	109	250	93	115	150	120	70	176
Serum bilirubin (highest value, mg. per 100 cc.)	5.1	5.0	—	27.5	6.5	10	15.5	8.6	—	9.2	10.8	—	—
Van den Bergh reaction	Direct immediate strong	Direct immediate strong	—	Direct immediate strong	Direct immediate strong	Direct immediate strong	Direct immediate strong	Direct immediate strong	—	Direct immediate strong	Direct immediate strong	—	—
Platelets (lowest count per cu. mm.)	—	—	—	226,000	30,000	153,000	—	121,770	—	56,000	534,870	—	—

COMMENT

The symptom complex of Weil's disease is often sufficiently characteristic to permit the condition to be diagnosed clinically. The onset is abrupt, with chills, fever, headache, muscular pains and weakness. In the present series a true chill

TABLE 2.—*Cerebrospinal Fluid in Weil's Disease*

				Cerebrospinal Fluid							Blood	
Patient	Case	Day of Illness	Rigidity of Neck	Color	Bilirubin, Mg. per 100 Cc.	Van den Bergh Reaction	Globulin	White Cells per Cc.	% of Polymorphonuclear Cells	Sugar, Mg. per 100 Cc.	Icterus Index, Units	Bilirubin, Mg. per 100 Cc.
Cases with Meningismus												
J. E.	1	7	++++	Golden yellow	—	—	0	52	50	83	—	—
		8	++++	Golden yellow	—	—	0	990	90	71	—	—
		10	+++	Pale yellow	—	Direct, immediate, weak	Slight trace	142	18	63	54	5.1
		19	0	Colorless	—	—	0	13	5	89	19	—
L. D.	2	3	++	Colorless	—	—	0	1	0	91	35	—
		6	++	Yellow	—	—	Faint trace	242	19	50	—	—
		9	+	Blood tinged	—	—	—	12	—	56	60	5
		10	0	Blood tinged	—	—	—	38	0	—	40	3
L. G.	10	3	+++	Colorless	—	—	0	2	0	91	—	—
		16	+	Golden	0.6	Direct, immediate, weak	0	4	0	81	120	11
Cases without Meningismus												
T. J.	3	11	0	Pale yellow	—	—	Slight trace	14	15	65	64	—
A. J.	4	13	0	Golden yellow	0.55	Direct, immediate, weak	0	12	0	105	300	21.2
E. H.	5	10	0	Golden yellow	0.56	Direct, immediate, weak	+	93	18	77	94	9.6
E. Tr.	6	10	0	Pale yellow	0.33	Direct, immediate, weak	Slight trace	94	6	67	109	8.3
E. Tu.	7	6	0	Lemon yellow	Too low to read	Direct, immediate, 8 minutes	Slight trace	81	24	59	250	15.5
F. H.	13	21	0	Colorless	—	—	0	0	0	83	20	—
H. G.	8	15	0	Pale yellow	Too low to read	Direct, immediate, weak	0	81	80	59	93	8.6
G. H.	9	8	0	Pale yellow	Too low to read	Direct, immediate, weak	+++	40	90	63	115	—

occurred in 6 cases, chilly sensations in several more and fever in all 13. Muscular pains, headache, nausea and weakness each occurred in 11. Emesis was present in 10 and cough and abdominal pain each in 6. External bleeding was observed in 3 and convulsions in 1. The occurrence of symptoms referable to the urinary tract was also of interest, for 5 patients experienced frequency and 3 dysuria. Four patients were troubled with persistent hiccups. In each of these patients there was marked retention of urea, and the singultus stopped as the blood urea approached normal.

Physical examination revealed jaundice in all 13 cases, tenderness of the muscles of the calves in 12, conjunctival injection in 11, abdominal tenderness in 9, hemorrhagic manifestations in 8, enlargement of the liver in 8, skin eruption in 3, meningismus in 3, generalized lymphadenopathy in 2, iridocyclitis in 1 and auricular fibrillation associated with pericardial friction rub in 1. Abdominal tenderness when present was in the right upper quadrant and occurred in those cases with enlargement of the liver. It was thought to be due to the distention of Glisson's capsule.

Perusal of charts 3 and 4 reveals that the delayed auriculoventricular conduction in case 8 (chart 3) and the pericarditis and auricular fibrillation in case 10 (chart 4) each occurred during the height of the illness, when retention of urea was most marked. While it is possible that the uremia was responsible for the pericarditis, it seems more likely that the auricular fibrillation and the disturbance of conduction were due to the effect on the heart of the spirochetes or their toxic products, for we have not noted such cardiac involvement in uremia from other causes.

The significant findings in the blood and the urine are summarized in table 1. There is still uncertainty as to the course of the hemorrhagic manifestations in this disease. The prothrombin percentages, as determined by the method of Quick,[12] were appreciably decreased in most instances. They did not, however, reach levels sufficiently low to account for the hemorrhagic manifestations. In the 3 cases in which platelet counts were performed, thrombopenia was not marked enough to account for hemorrhage. A positive Rumpel-Leede test in case 11 indicated the presence of capillary damage. This test also was negative in the other cases with hemorrhage. A considerable leukocytosis, with counts usually between 18,000 and 30,000, was present in 11 of the 13 cases. There was a distinct shift to the left in the leukocytes of the peripheral blood as well as in the bone marrow in the 2 patients subjected to sternal puncture. In 4 patients a marked hypochromic, microcytic anemia developed. Albuminuria was present in every case. Microscopic study of the urine not uncommonly revealed white cells, red cells or both. Levels of urinary urobilinogen were extremely variable.

Marked retention of the nitrogenous products of the metabolism of protein was common in this series as in others of Weil's disease. There has been some question as to the genesis of azotemia in this condition.[13] Reference to table 1 shows that frequently the blood urea was higher in the moderately jaundiced patients than in those more deeply icteric. The cases illustrated in figures 3 and 4 each showed a precipitous fall in blood urea concomitant with a rise in icterus index. As a result of these observations we believe that the renal damage, which was obviously quite transient, was due to the effect of the spirochetes or their products, rather than to cholemia.

Three of the 13 patients (cases 1, 2 and 10) exhibited clinical signs of meningeal involvement. These consisted of marked stiffness of the neck, Kernig and Brudzinski signs, headache and vomiting. The patient in case 1 had in addition generalized epileptiform convulsions. The cell count on the cerebrospinal fluid of this patient reached a peak of 990 cells per cubic millimeter of fluid. Polymorphonuclear cells predominated early and lymphocytes later (chart 1). Case 10, in which considerable rigidity of the neck preceded the appearance of jaundice, was mistaken for a case of tuberculous meningitis on admission of the patient to the hospital. This case demonstrates that marked meningismus may exist without any abnormality of the

12. Quick, A. J.: The Nature of Bleeding in Jaundice, J. A. M. A. **110**:1658-1662 (May 14) 1938.

13. Merklen, P., and Lioust, C.: L'azotémie dans les icteres infectieux, Bull. et mém. Soc. méd. d. hôp. de Paris **40**:1865-1916 (Nov. 24) 1916.

cerebrospinal fluid other than an increase in pressure. Similar American cases have been reported by Haschec and Tobey [14] and Ashe, Pratt-Thomas and Kumpe.[2b] Seven of the 8 remaining cases in which the patient was subjected to lumbar puncture showed an increased cell count for the cerebrospinal fluid in spite of the absence of clinical signs of meningeal involvement. In 5 of these the protein content of the cerebrospinal fluid was also increased. It is of interest that such changes occurred without clinical symptoms, whereas in case 10 clinical meningismus occurred without abnormality of the cerebrospinal fluid. Inasmuch as the lumbar punctures in this case were performed on the third and sixteenth days, the possibility of a transient pleocytosis of the cerebrospinal fluid in the interim cannot be excluded. The dextrose content of the cerebrospinal fluid was essentially normal in all of the cases studied.

A yellow cerebrospinal fluid was obtained in 10 of the 11 cases in which lumbar puncture was performed. In some of these the yellow color faded somewhat on standing, and in case 3 it disappeared completely. In 8 cases the cerebrospinal fluid gave a positive qualitative van den Bergh reaction, and in 4 it was possible to measure the bilirubin content quantitatively. This proves to our satisfaction that at least in Weil's disease bilirubin in appreciable quantities passes the meningeal barrier. Since we found more bilirubin in the cerebrospinal fluids of patients with Weil's disease than in patients jaundiced to like degrees in other diseases, we agree with Drägert's [15] hypothesis that the permeability of the diseased meninges in this condition is increased.

SUMMARY

Thirteen cases of Weil's disease are reported. In 2 both clinical and laboratory evidence of meningitis was observed; in 7 there was an abnormal cellular reaction in the cerebrospinal fluid without clinical signs of meningeal irritation, and in 1 meningismus was present without the cerebrospinal fluid showing pleocytosis.

Cell counts on the cerebrospinal fluid may reach 1,000 or more per cubic millimeter. Polymorphonuclear cells predominate early and lymphocytes later. The dextrose content of the cerebrospinal fluid is not altered. Yellow discoloration of the cerebrospinal fluid is common in Weil's disease. It is at least in part due to bilirubin.

Marked retention of urea is frequent.

Pericarditis, auricular fibrillation or disturbances of conduction may occur in hearts previously normal.

The plasma prothrombin, although appreciably decreased in most instances, usually does not reach levels sufficiently low to account for the hemorrhagic manifestations.

Anasarca, the result of hypoproteinemia, may develop.

Immunotransfusions may be of value in treatment and are worthy of a more extended trial.

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14. Haschec, W., and Tobey, F. J.: A Case of Weil's Disease, J. A. M. A. **113**:1319-1321 (Sept. 30) 1939.

15. Drägert, E.: Beitrag zur pathologischen Anatomie der Weilschen Erkrankung, Virchows Arch. f. path. Anat. **292**:452-464 (June) 1934.

PENTOSURIA ASSOCIATED WITH DIABETES MELLITUS

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There has been no evidence to show that essential pentosuria is related in any way to diabetes mellitus, and no complete report of their combined occurrence can be found in the literature.[1] In the first case presented here the patient was suffering from both essential pentosuria and diabetes mellitus. By way of comparison a case of uncomplicated essential pentosuria is also reported.

Essential pentosuria is a hereditary abnormality of metabolism characterized by continuous excretion of small amounts of pentose in the urine, unaffected by alterations in the diet. The first case of this disorder was reported by Salkowski and Jastrowitz [2] in 1892. Since then reports of more than 170 cases have appeared in the literature. The incidence of this disorder in the general population is estimated by Blatherwick [3] to be 1 : 50,000.

The pentose excreted has been found in most instances to be levorotatory xylulose, formerly called *l*-xyloketose. Enklewitz and Lasker [4] have shown that the administration of *d*-glucuronic acid caused an increased excretion of xylulose, and they were in this way led to believe that glucuronic acid is a precursor of xylulose. Schultsz [5] has confirmed this work and suggested that the reaction may take place in the kidney.

Pentosuria can be classified into two types, alimentary and essential. Alimentary pentosuria is the transient excretion of pentose in the urine following the ingestion of certain foods, particularly cherries, grapes, prunes, pears, blackberries, strawberries, wine and beer. These foods contain pentosans, some of which are excreted in the urine in the form of pentose. In many cases pentosuria which has been designated transient, intermittent, occasional or acquired falls under this heading of alimentary pentosuria.

The criteria for the diagnosis of essential pentosuria are as follows: (1) the continuous excretion of small amounts of pentose in the urine, unrelated to diet; (2) absence of symptoms; (3) history of hereditary pentosuria when obtainable, and (4) a normal dextrose tolerance curve unless there is associated diabetes mellitus.

For the identification of pentose the following tests should be performed: (1) the reduction of copper salt solutions, (2) test for absence of fermentation, (3) the

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1. Since this article has been written, a case of pentosuria and diabetes mellitus has been reported (Moss, R. E., and Walker, B. S.: Pentosuria and Diabetes Mellitus, J. A. M. A. **120**: 25 [Sept. 5] 1942).

2. Salkowski, E., and Jastrowitz, M.: Ueber eine bisher nicht beobachtete Zuckerart im Harn, Centralbl. f. d. med. Wissensch. **30**:337, 1892.

3. Blatherwick, N. R.: Xylulosuria, in Blumer, G.: Practitioners Library of Medicine and Surgery, New York, D. Appleton-Century Company, Inc., 1938, vol. 13.

4. Enklewitz, M., and Lasker, M.: The Origin of *l*-Xyloketose (Urine Pentose), J. Biol. Chem. **110**:443, 1935.

5. Schultsz, J. C.: Ondersoekingen over pentosurie, Amsterdam, N. V., Uitgevers-Maatschappij "Kosmos," 1938.

test with Bial's reagent (orcinol, hydrochloric acid and ferric chloride), (4) the aniline acetate test [6] and (5) preparation of xylulosazone. Familiarity with the peculiar characteristic behavior of pentose with the copper reducing salts is helpful. It is commonly observed that when urine containing pentose is heated over a flame with copper salts, reduction does not take place immediately, as it does with dextrose. However, xylulose will reduce copper salt solutions at room temperature.[7] This is a valuable confirmatory test. Although the reaction will be obtained in two to three hours or less, it is a practice in some clinical laboratories to allow the solution to stand overnight, the reaction being noted the following morning.

Lasker and Enklewitz [7] have also found that a yellow precipitate is formed with xylulose in Benedict's solution at 55 C. in ten minutes. Furthermore, urine containing xylulose retains its reducing powers indefinitely on standing, which is not true of urine containing dextrose, since the latter sugar undergoes glycolysis.

If the tests just listed yield positive reactions and the confirmatory reactions with the copper salt solutions are present, it is hardly necessary to attempt to obtain the specific osazone.

The daily excretion of pentose usually does not exceed 2 to 4 Gm. Occasionally, smaller amounts are obtained. Solis-Cohen and Gershenfeld [8] reported a case in which an elderly man with essential pentosuria had been observed for twenty-seven years and at the end of this time was excreting 10.5 Gm. of pentose daily. Whatever the amount excreted, it remains constant for each person with small variations dependent on the total output of urine for twenty-four hours.

REPORT OF TWO CASES

CASE 1.—*Essential pentosuria associated with diabetes mellitus.*

L. M., a Russian Jew aged 52, was originally seen in the orthopedic clinic of the hospital on Dec. 1, 1937, complaining of cramps in the calves of the legs, occurring mainly at night. The blood pressure at this time was 115 systolic and 70 diastolic, measured in millimeters of mercury. Calcium salts were prescribed, and he was not seen again until Nov. 8, 1940, when he complained of substernal pain which was increased with exertion. His weight was found to be 174 pounds (79 Kg.). The blood pressure was 155 systolic and 90 diastolic in millimeters of mercury. Examination of a specimen of urine at this time yielded the following data: specific gravity, 1.018; sugar, a trace (Benedict's solution); acetone, none, and albumin, none. Microscopic examination of the urine revealed occasional blood cells, both white and red. The urine was retested with Benedict's quantitative solution and was found to contain 0.8 per cent sugar. The cramps in the calves of the legs were still present. Examination of the lower extremities failed to reveal any evidence of peripheral vascular disease. When the patient was examined again, in September 1941, the blood pressure was 160 systolic and 105 diastolic in millimeters of mercury and continued at about this level on his subsequent visits to the clinic. The weight was reduced to 165 pounds (75 Kg.). The patient was seen periodically during 1941 and complained of frequent attacks of substernal pain lasting ten minutes and associated with dyspnea on exertion. A specimen of urine tested in December 1941 with Benedict's quantitative solution contained 0.5 per cent sugar. The blood pressure at this time was 190 systolic and 110 diastolic in millimeters of mercury. When the patient was seen again, in March 1942, it was decided to study the urine for the nature of the reducing substance. The urine was found to contain pentose. No dextrose was present in individual or in twenty-four hour specimens of urine. Samples of blood drawn while the patient was fasting contained 150 mg. of sugar per hundred cubic centimeters on two occasions. Repeated examinations of single specimens of urine revealed between 0.15 and 0.3 per cent pentose but no dextrose. Dextrose tolerance curves obtained on two occasions (100 Gm. of dextrose fed) were of the diabetic type (table 1).

6. Reiner, M.: Manual of Clinical Chemistry, New York, Interscience Publishers, Inc., 1941.

7. Lasker, M., and Enklewitz, M.: A Simple Method for the Detection and Estimation of *l*-Xyloketose in Urine, J. Biol. Chem. **101**:289, 1933.

8. Solis-Cohen, S., and Gershenfeld, L.: Essential Pentosuria of Twenty-Eight Year's Standing, Am. J. M. Sc. **192**:610, 1932.

The sugar found in the urine was not fermented by bakers' yeast. It reduced copper salt solutions in two to three hours at room temperature and in ten minutes at 55 C. Positive reactions with Bial's reagent and a positive reaction with aniline acetate were obtained with every specimen, and xylulosazone was obtained with phenylhydrazine.

Comment.—This patient was apparently suffering from mild diabetes mellitus but did not experience any of the cardinal symptoms of the disease. At the same time, pentose was being excreted in constant amounts persistently in the urine and all the criteria for the diagnosis of essential pentosuria were satisfied. It is of interest that in this case the nature of the reducing substance in the urine was studied before the blood sugar level was obtained. If the blood sugar level had been obtained first, the patient might have been considered solely to have mild diabetes, and investigation of the nature of the urinary sugar might not have been undertaken.

Fischer and Reiner [9] studied 4 children with essential pentosuria and obtained dextrose tolerance and xylose tolerance curves. They determined the total blood sugar levels; the dextrose was then fermented, and the nondextrose reducing substances were obtained in this way. After xylose was fed, its level in the blood

TABLE 1.—*Dextrose Tolerance of a Patient with Diabetes Mellitus and Associated Essential Pentosuria (Case 1)*

Date	Time in Relation to Ingestion of 100 Gm. of Dextrose	Blood Sugar, Mg./100 Cc.	Urine Sugar, Percentage
4/2/42	Before (patient fasting)	181	Trace
	½ hour after	276	1.8
	1 hour after	306	6.6
	1½ hours after	222	10.0
	2 hours after	161	2.2
4/20/42	Before (patient fasting)	162*	0.2
	½ hour after	270*	0.8
	1½ hours after	310*	5.5
	2½ hours after	250*	6.6

* All specimens of blood contained 20 mg. of nonfermentable nondextrose reducing substances per hundred cubic centimeters.

could be determined by noting the increase in the nondextrose reducing substance over values obtained on blood drawn while the patient was fasting. They found that the feeding of dextrose had no effect on the urinary excretion of xylose, while the dextrose tolerance curve remained unaltered when xylose was fed. The total nondextrose reducing substances remained the same in the blood of normal persons as well as in that of persons with essential pentosuria. The nondextrose reducing substances in the blood in this case were determined and found to remain constant at 20 mg. per hundred cubic centimeters in all specimens taken during the determination of the dextrose tolerance curve (table 1). Thus the elevation of the blood sugar was due to the elevation of the dextrose portion of the total sugar and not of the nondextrose reducing substances.

CASE 2.—*Essential pentosuria.*

A. L., a Russian Jew aged 41, was admitted to the medical clinic on Aug. 29, 1941, complaining of attacks of weakness and faintness lasting a few seconds and occurring for the past eight months. There had been a loss of 9 pounds (4 Kg.) in weight over a five month period. Examination failed to reveal any major abnormalities. There was a short, rough systolic murmur at the apex of the heart. The blood pressure was 126 systolic and 78 diastolic measured in millimeters of mercury. The first examination of the urine yielded the following data:

9. Fischer, A. E., and Reiner, M.: Pentosuria in Children, Am. J. Dis. Child. **40**:1193 (Dec.) 1930.

specific gravity, 1.028; albumin, none, and sugar, present (3 plus). In September 1941 a sample of blood drawn while the patient was fasting contained 98 mg. of sugar per hundred cubic centimeters. The dextrose tolerance test (100 Gm. of dextrose fed) yielded a high normal curve which returned to the fasting level in two hours. On the basis of these data a tentative diagnosis of renal glycosuria was made. The dextrose tolerance test was repeated in June 1942, and the curve was found to be entirely normal (table 2). The urine was studied, and the reducing substance was proved to be xylulose.

COMMENT

Essential pentosuria should be suspected when small amounts of a reducing substance are found constantly in the urine of a person who has normal blood sugar levels and no diabetic symptoms. A pentose can be identified by the special tests that have been described.

Reactions similar to those obtained with pentose in the urine are also given by glucuronates. These substances may be present in small quantities in normal urine and may be present in larger amounts after the ingestion of certain drugs, such as chloral hydrate, camphor, menthol, oil of turpentine, phenol, acetanilid and some alkaloids. Glucuronates are usually present in conjugated form, resulting from combination of an ingested drug and glucuronic acid. Protas [10] noted an example of "toxic pentosuria" in a person addicted to morphine. When the

TABLE 2.—*Dextrose Tolerance of a Patient with Essential Pentosuria (Case 2)*

Date	Time in Relation to Ingestion of 100 Gm. of Dextrose	Blood Sugar, Mg./100 Cc.
9/16/41	Before (patient fasting)	115
	½ hour after	190
	1 hour after	160
	1½ hours after	112
	2 hours after	83
6/11/42	Before (patient fasting)	110
	½ hour after	158
	1 hour after	126
	1½ hours after	106
	2 hours after	91

morphine was withdrawn, the pentosuria disappeared. It may well have been due to glucuronates.

Conjugated glucuronates do not give reactions in all the tests for pentose. Free glucuronic acid, on the other hand, gives a reaction in the majority of these tests and as a result is almost indistinguishable from pentose, Glucuronic acid is set free after prolonged heating or in the presence of the concentrated acids used in the Bial and the aniline acetate test.

It is apparent that conjugated glucuronates or free glucuronic acid will be confused with pentose unless careful observation reveals that all the tests do not readily yield positive results. In addition, the excretion of glucuronates may be directly related to the ingestion of a drug and can in this way be controlled.

There are no known symptoms that are considered the direct result of essential pentosuria. Garrod [11] has said that if the metal-reducing tests were not everyday practice in medical work, there would be no symptom by which the existence of pentosuria could be suspected. Margolis [12] found that some of his patients with pentosuria suffered from migraine. In the 2 cases presented here the patients did not have symptoms of migraine, and there is no mention of migraine in the majority of reports of cases of essential pentosuria.

10. Protas, M.: Pentosuria, South. Med. & Surg. **96**:154, 1934.
11. Garrod, A. E.: Inborn Errors of Metabolism, ed. 2, London, Milford, 1923.
12. Margolis, J. I.: Chronic Pentosuria and Migraine, Am. J. M. Sc. **177**:348, 1929.

Essential Pentosuria and Renal Glycosuria.—The diagnosis usually made when essential pentosuria is not recognized is renal glycosuria (renal diabetes, or "benign" glycosuria). Two of the 3 cases of essential pentosuria reported by Marble [13] were originally considered to have been instances of renal glycosuria. Enklewitz and Lasker [14] reported the occurrence of essential pentosuria in twins; one was treated in childhood for renal diabetes and the other for "juvenile diabetes." Many other reports of cases of essential pentosuria reveal that the usual diagnosis prior to the discovery of the true nature of the sugar was renal diabetes.

In both renal glycosuria and essential pentosuria, both of which are rare, the excretion of the sugar is constant and is essentially independent of diet. In both conditions the dextrose tolerance curves are normal, except in rare instances when diabetes mellitus may be associated coincidentally.[15] The amount of excretion for each individual specimen of urine is usually under 1 per cent in essential pentosuria and over 1 per cent in renal glycosuria. In both disorders, the symptoms of diabetes are absent and there is no progression to diabetes mellitus. Finally, the nature of the reducing substance is different, and the fermentation test will indicate whether it is dextrose or pentose. Jones and Sussman [16] emphasized that in both conditions the renal and the pancreatic functions are normal.

Essential Pentosuria and Diabetes Mellitus.—Ever since the original article on pentosuria by Salkowski and Jastrowitz [2] in 1892 the question had arisen whether there was any relation between essential pentosuria and diabetes mellitus. Garrod [11] stated that he considered essential pentosuria one of the "inborn errors of metabolism" along with alkaptonuria, cystinuria, porphyrinuria and congenital steatorrhea.

The early literature on the subject is confusing. Several authors reported finding pentosuria frequently in persons with severe diabetes (Külz and Vogel,[17] Pedrazzini [18] and Voit [19]). Thus Külz and Vogel [17] were able to find in the urine of some of their patients with severe diabetes, in addition to a glucosazone, an osazone with the melting point and the nitrogen content of pentosazone. However, they required several liters of urine to obtain a small yield of the substance. Voit [19] admitted the difficulty of separating chemically small amounts of pentose from dextrose when both are present in the same specimen of urine. He reported finding an osazone with the melting point of pentosazone in the urine of 12 of the 14 patients with severe diabetes whom he studied. Bendix [20]; Joslin and associates [21]; Enklewitz and Lasker; Blatherwick; one of us (M. R.), and many others have searched for pentose in the urine of persons with diabetes and have been unable to detect it in any constant amount in mildly or severely diabetic persons. It is assumed that the substance that was considered a pentose by these earlier investigators was probably a glucuronate.

13. Marble, A.: Chronic Essential Pentosuria, Am. J. M. Sc. **183**:827, 1932.

14. Enklewitz, M., and Lasker, M.: Pentosuria in Twins, J. A. M. A. **105**:958 (Sept. 21) 1935.

15. Curran, J. A., and Mills, C. A.: Report of a Case of Renal Diabetes Associated with Diabetes Mellitus, J. Lab. & Clin. Med. **13**:646, 1928.

16. Jones, H. W., and Sussman, W.: Renal Glycosuria and Pentosuria, Am. J. M. Sc. **173**:513, 1927.

17. Külz, E., and Vogel, J.: Ueber das Vorkommen von Pentosen im Harn bei Diabetes Mellitus, Ztschr. f. Biol. **14**:185, 1895.

18. Pedrazzini, F.: La ricerca dei pentosi nelle orine; pentosurie e pseudopentosurie, Gior. d. r. Soc. ital. d'ig. **25**:241, 1903.

19. Voit, W.: Ueber das Vorkommen von Pentosen in diabetischen Harnen, Ztschr. f. phys. u. diätet. Therap. **12**:659, 1908-1909.

20. Bendix, E.: Ein Fall von Pentosurie, München. med. Wchnschr. **50**:1551, 1903.

21. Joslin, E. P.; Root, H. F.; White, P., and Marble, A.: The Treatment of Diabetes Mellitus, ed. 7, Philadelphia, Lea & Febiger, 1940.

There are many individual case reports in the literature concerning patients with diabetes mellitus who in the course of their illness were discovered to have pentose in the urine intermittently (Kaplan,[22] d'Amato [23] and Zlataroff [24]). In the case reported by Kaplan,[22] the excretion of "pentose" was not constant and many specimens of urine were free of "pentose." In the case reported by Rosenbloom,[25] "pentose" was encountered on one occasion and lactose was also found in the urine. In these and other cases the reports indicate conclusively that the substances found were appearing in the urine only intermittently and were not proved to be pentose.

Joslin and associates [21] in spite of a careful search for cases of essential pentosuria have recorded only 9 instances of this disorder. In 1 case, the patient had occasional blood sugar values slightly above normal and the condition has been difficult to classify. Other than this questionable case they have not encountered any instances of the association of diabetes mellitus and essential pentosuria. Blatherwick [26] has observed 1 case of this kind, but it has been incompletely studied and has not been reported. In this case only one specimen of urine had been examined, and it was found to contain 2.03 per cent dextrose and 0.16 per cent pentose.

The clinical importance of recognizing essential pentosuria has been stressed many times before. Patients with essential pentosuria require no treatment except for the reassurance that they do not have diabetes mellitus. They should be told the nature of the reducing substance in their urine to facilitate future examinations in new locations and acquainting physicians under whose care they may come with the diagnosis. In addition, when the rare coincidental association of diabetes mellitus and essential pentosuria exists, the failure to discover both will result in difficulties in treatment. The failure to recognize the diabetes mellitus will carry along with it the dangers of developing complications common in untreated diabetes mellitus of long standing. On the other hand, failure to recognize the presence of essential pentosuria will cause confusion, as sugar will always be present in the urine despite seemingly adequate control with diet and insulin.

The harm that is done to a person who has essential pentosuria and is treated for diabetes mellitus is obvious.

SUMMARY AND CONCLUSIONS

Two cases of essential pentosuria are presented and discussed.

The coexistence of diabetes mellitus with essential pentosuria was discovered in 1 of these cases.

Essential pentosuria and diabetes mellitus are distinct entities and seem to bear no relation to each other.

Dr. Louis J. Soffer assisted us during this investigation.

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22. Kaplan, D. M.: Intermittent Pentosuria and Glycosuria, New York M. J. **84**:233, 1906.

23. d'Amato, L.: Su di un caso di calcolosi pancreatica con glicosuria e pentosuria, Riv. crit. di clin. med. **3**:513, 1902.

24. Zlataroff, A.: Ueber eine neue Art von Glykosurie: Glukosomethylpentosurie, Ztschr. f. physiol. Chem. **97**:28, 1916.

25. Rosenbloom, J.: Report of a Case of Diabetes Mellitus Complicated by Occasional Pentosuria and Lactosuria, J. A. M. A. **64**:508 (Feb. 6) 1915.

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CLINICAL EXPERIENCE WITH MIXTURES OF PROTAMINE ZINC AND UNMODIFIED INSULINS

A PRELIMINARY REPORT

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All physicians who treat diabetes mellitus have long been interested in the perfecting of some type of delayed action insulin which would adequately control the level of sugar in the blood when injected once in each twenty-four hours. It was hoped that protamine zinc insulin, introduced in 1936 by Hagedorn and his associates [1] would be the answer to the problem of a depot of insulin. However, further experience with this type of insulin revealed that a single injection in each twenty-four hours was incapable of giving satisfactory control of the blood sugar in many cases of severe diabetes. In such cases it was often not possible to give sufficient protamine zinc insulin to control postprandial hyperglycemia during the day without producing nocturnal insulin reactions. Consequently, most authors have agreed that for satisfactory control of severe diabetes mellitus protamine zinc insulin must be supplemented by unmodified insulin.[2] In this scheme of treatment, the protamine zinc insulin is said to supply the patient's basal requirements, that is, the requirements for his endogenous carbohydrate metabolism.[3] Unmodified insulin is given during the day to supply the additional need arising from the ingestion of food (exogenous requirement).

The exact time and the manner of the administration of supplementary unmodified insulin have not been generally agreed on. Some authorities [4] prefer that the unmodified insulin be given in a separate injection. However, the convenience to the patient of a single injection each day has led to recommendation by several authors that the two insulins be injected together.

The use of such mixtures was first proposed by Lawrence and Aitken,[5] in 1938. In 1939 Lawrence [6] outlined a method of mixing the two types in the same syringe. Included in his report are the results of a series of determinations of

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1. Hagedorn, H. C.; Jensen, B. N.; Krarup, N. B., and Wodstrup, I.: Protamine Insulinate, J. A. M. A. **106**:177-180 (Jan. 18) 1936.

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3. Martin, H.; Drury, D. R., and Strouse, S.: Basal Insulin Requirement in Diabetes Mellitus, Arch. Int. Med. **66**:78-92 (July) 1940. Ricketts, H. T.: The Constancy of Action of Protamine Zinc Insulin, Am. J. M. Sc. **201**:51-59 (Jan.) 1941.

4. Wauchope, G. M.: Zinc Protamine Insulin and Soluble Insulin: Interaction in Combined Doses, Lancet **1**:962-966 (May 25) 1940. Masters, T. D.: The Uses of the Newer Insulins, Illinois M. J. **78**:319-323 (Oct.) 1940. Smith, B., and Grishaw, W. H.: Survey of Diabetes: Statistical Data and Control Comparisons with Various Insulins, Arch. Int. Med. **66**:465-477 (Aug.) 1940.

5. Lawrence, R. D., and Aitken, R. S.: Discussion on the Value of Zinc Protamine Insulin in Treatment, Proc. Roy. Soc. Med. **31**:1217-1218 (Aug.) 1938.

6. Lawrence, R. D.: Zinc Protamine-Insulin in Diabetes: Treatment by One Daily Injection, Brit. M. J. **1**:1077-1080 (May 27) 1939.

the blood sugar of diabetic patients made at definite intervals after the injection of various mixtures. However, he did not hazard an opinion as to how much of the unmodified insulin entered into combination with the excess of protamine. In commercial preparations of protamine zinc insulin, the excess of protamine has been variously estimated to be from 40 to 50 per cent. More extensive studies of the effect on the level of sugar in the blood have been made by Wauchope,[4] Ulrich [7] and Colwell.[8]

Wauchope pointed out that the effect of a combination of the two types of insulin was modified not only by the degree of their mixing but also by the relative proportions in which they were mixed, the total number of units injected, the final hydrogen ion concentration of the mixture and the reaction of the patient's tissues to the mixture. Although he agreed that injecting the two insulins together would give adequate control of the blood sugar for the next twenty-four hours, he stated that in his experience larger total doses of insulin were required when the two were given together than when they were given separately.

Ulrich studied the effect on blood sugar of administering various mixtures of protamine zinc and unmodified insulins to diabetic patients who were either fasting or eating their usual diets, at various intervals after the injections. He concluded that in such a mixture the unmodified insulin was precipitated along with the protamine since a hypoglycemic effect was not obtained when the mixture was centrifuged and the supernatant fluid injected into a patient known to be insulin sensitive. However, since the injection of the mixture resulted in a much more rapid hypoglycemic effect than did the injection of the same total dose of protamine zinc insulin alone, he expressed the belief that the unmodified insulin had not entered into chemical combination with the excess of protamine to form protamine insulinate. He suggested that the hydrogen ion concentration of the acid solution of unmodified insulin was changed by the alkaline solution of protamine zinc insulin to near the isoelectric point of insulin; then the unmodified insulin precipitated along with the protamine zinc insulin. In his experience the injection of the mixtures of protamine zinc and unmodified insulin resulted in satisfactory control of the level of blood sugar. A mixture of 3 parts of the unmodified insulin with 2 parts of the protamine zinc insulin was, he reported, an optimal mixture.

Extensive experiments with the injection of mixtures of protamine zinc and unmodified insulins are at present being carried out by Colwell, of Evanston, Ill. In a personal communication to one of us (E. H. R.) he stated that mixtures of this type had effects on the blood sugar curves of diabetic patients which were intermediate between those of the two components of the mixtures. In his experience, satisfactory results were obtained when the mixture contained as much as 4 parts of unmodified insulin to each part of protamine zinc insulin. He raised the question whether or not these mixtures might have undergone a change due to the altered hydrogen ion concentration of the solution with formation of a new compound which had a different physiologic activity, possibly similar to that of solutions of soluble protamine insulin or globin insulin.

At the Mayo Clinic we have been using mixtures of the two types of insulin in the routine treatment of severe diabetes since Lawrence [6] published his observations. In our experience this method of treatment has proved satisfactory for a large proportion of diabetic patients. However, there are still cases in which adequate control of the diabetes has been difficult or impossible with this method.

7. Ulrich, H.: Clinical Experiments with Mixtures of Standard and Protamine Zinc Insulin, Ann. Int. Med. **14**:1166-1179 (Jan.) 1941.

8. Colwell, A. R.: Personal communication to the authors.

Furthermore, the question of which scheme of adjusting the amounts of each type of insulin gives the best results has not yet been answered. Masters stated: "The so-called 'educated guess' based on experience in handling a large diabetic service remains the most satisfactory solution to the problem of gauging insulin dosage." An "educated guess," however, can hardly solve the problem of the diabetic patient who daily must adjust his own dosage of insulin, nor can it serve the needs of the average physician who lacks the opportunity of becoming so adept. Since variations in the daily requirement of insulin in severe diabetes necessitate daily adjustment in dosage, we have attempted to devise some scheme for making these adjustments. None of the methods of adjustment which we have employed thus far has been entirely satisfactory. For this reason we have studied the effects on diabetic patients of injecting various mixtures. Our investigations were carried out along the lines suggested by the work of Ulrich, Wauchope and Colwell. In this paper we wish to make a preliminary report of our work, which as yet is limited.

CONDITIONS OF STUDY AND PROCEDURES

The scheme of treatment used in our studies conformed as closely as possible to that employed in the usual care of diabetic patients at the clinic.

Our observations were made on 2 young women who had severe diabetes. Each had been under our observation throughout most of the course of her illness. Neither presented any complications which might interfere with the interpretation of our results, and both consented to the special study.

These patients were admitted to our nutritional ward for a preliminary period of stabilization, lasting ten days in each instance, before the study was begun. They were placed on standard diabetic diets, the caloric content of which was determined by calculations based on their age, height and ideal weight from tables which had been prepared by Boothby and Berkson.[9] The total daily allowance of food was divided into three meals of ordinary size, given at 8 a. m., 12 noon and 5 p. m., and one small feeding at 9 p. m. All of the food was weighed and prepared in the kitchen attached to the nutritional ward. The mineral content of each of the menus was known, and since these were rotated every three days, we believe that a reasonably constant mineral balance was maintained throughout the period of observation. The sodium chloride content of the diet was maintained at approximately 10 Gm. daily; 5 or 6 Gm. was contained in the food, and 4 or 5 Gm. was given in a saltcellar to be added to the food as the patient desired. The total daily allowance of fluid was kept at 2,000 cc. The intake and the output of fluids in each case were measured each day, and a satisfactory fluid balance was found to be maintained.

The patients were ambulatory and were encouraged to engage in activities similar to those which they ordinarily performed at home. No medication other than insulin was given to either patient. Both remained in good spirits and excellent health throughout the period of observation.

Each day four single specimens of urine, obtained at 6 a. m., 11 a. m., 4 p. m. and 9 p. m., were analyzed qualitatively for sugar. In addition, each twenty-four hour specimen of urine was analyzed quantitatively for dextrose.

The mixtures of the two types of insulin were given half an hour before breakfast unless otherwise specified. The site of injection was changed each day. In drawing the insulin into the syringe, the unmodified insulin was taken in first, the protamine zinc insulin second. No particular attempt was made to mix the two insulins more thoroughly since it had not been our custom to do so in the past. Both types of insulin were used in the strength of 80 units per 1 cc. Since we used protamine zinc insulin from one lot for the whole study, we believe that the excess of protamine per unit of protamine zinc insulin in each mixture injected was approximately the same amount.

The dosage of insulin was adjusted during the preliminary period of observation in accordance with the rules outlined by Wilder.[10] Briefly, the dose of protamine zinc insulin was determined by an analysis of the urine made at 6 a. m. and the dose of unmodified insulin by an analysis made at 4 p. m. In each instance the dose of insulin was reduced when the reaction was 0 or grade 1+, was left the same when the reaction was grade 2+

9. Boothby, W. M., and Berkson, J., cited by Wilder.[10]

10. Wilder, R. M.: A Primer for Diabetic Patients, ed. 7, Philadelphia, W. B. Saunders Company, 1941.

and was increased after a reaction of grade 3 to 4+. No supplementary doses of insulin were given during the day. By this method we were able to arrive at a reasonably constant total dose of insulin which would be satisfactory for each patient. The figure for this dose having been obtained in each instance, it was possible arbitrarily to give the total dose in various mixtures representing a series of ratios of protamine zinc to unmodified insulin. Changes in these ratios were made every fourth day. The concentrations of blood sugar were determined in series on the third day of administration of each ratio. By placing this interval between each series of determinations we hoped to eliminate the influence on the level of the blood sugar of the protamine zinc insulin in the preceding dosage.

The method used in determining the level of the blood sugar on the days selected was as follows: Samples of capillary blood were taken half an hour preceding and one hour following each meal, and twenty-four hours after the injection of the mixture being studied. The dextrose content of the blood samples was determined by a micromethod. We have plotted the blood sugar levels obtained in this manner as curves in order to compare the results of all observations. Such a series will be referred to hereafter in this paper as a "blood sugar curve." This is to be distinguished from the usual curve obtained from the sugar tolerance test. Occasionally, in order to determine the average trend of the blood sugar level from several series of determinations, the values which form the basis of several curves have been averaged and plotted. These average values and the resultant curve will be referred to as the "mean" curve hereafter in this paper.

RATIO OF PROTAMINE ZINC INSULIN TO UNMODIFIED INSULIN USED IN 100 CASES

As a preliminary to consideration of the results obtained in our special study of 2 patients, we should like to include the results of a study of the dosage of

Ratio of Protamine Zinc Insulin to Unmodified Insulin in the Total Dose of One Hundred Diabetic Patients

	Total Daily Dose							
	Less Than 20 Units		20-40 Units		40 or More Units		Entire Group	
Ratio *	Cases	Per Cent	Cases	Per Cent	Cases	Per Cent	Cases	Per Cent
1:1	23	65.7	4	8.5	..	....	27	27
1:2	3	8.6	14	29.8	8	44.4	25	25
1:3	..	....	13	27.6	5	27.8	18	18
1:4	..	....	2	4.3	..	....	2	2
1:5	..	....	1	2.1	..	....	1	1
1:6	..	....	1	2.1	..	....	1	1
2:3	9	25.7	10	21.3	2	11.1	21	21
2:5	..	....	2	4.3	2	11.1	4	4
4:5	..	....	..	....	1	5.6	1	1
Total	35	100	47	100	18	100	100	100

* Ratio of protamine zinc insulin to unmodified insulin.

insulin in 100 cases of diabetes taken at random from the files. The disease in these cases was severe enough to require the administration of a mixture of both types of insulin. We were interested in discovering which ratio or ratios were most often arrived at in these cases when satisfactory control was obtained.

The results of this preliminary study are summarized in the accompanying table. If a total of less than 20 units of insulin was required daily, the commonest ratio observed was that of 1 part protamine zinc insulin to 1 part of unmodified insulin; if a total of 20 to 40 units was required, the most frequently encountered ratios were 1:2, 1:3 and 2:3; if a total of 40 or more units was required, ratios of protamine zinc insulin to unmodified insulin of 1:2 and 1:3 were most common. If then the entire series was taken together as a group, with the amounts of insulin required in each case being disregarded, the numbers of cases in which the diabetes was controlled satisfactorily with mixtures representing ratios of the protamine zinc insulin to unmodified insulin of 1:1, 1:2, 1:3 and 2:3 were approximately equal.

Thus it appears that there is no optimal ratio of the two types of insulin which is automatically arrived at by the method of adjustment of insulin dosage which we have been using. However, ratios of the protamine zinc insulin to the unmodified insulin of 1:2, 1:3 or 2:3 apparently come nearest to an ideal mixture.

RESULTS

CASE 1.—The patient was an unmarried woman aged 19 years, whose diabetes had developed in 1932 after an attack of acute pharyngitis. A paternal aunt and uncle and one brother also had diabetes. The patient herself had been under a dietary and insulin regimen since the onset of her diabetes but had been repeatedly in trouble because of frequent acute infectious diseases and frequent lapses in the management of her diabetes. On four occasions, the last one in 1940, she had been in severe acidosis; twice the acidosis was so severe that it produced coma.

At the time of her admission to the nutritional ward, in November 1941, she was 62 inches (152 cm.) in height and weighed 139 pounds (63 kg.). General physical examination, examination of the ocular fundi and routine laboratory studies, including a roentgen study of the thorax and a flocculation test of the blood, revealed nothing of significance.

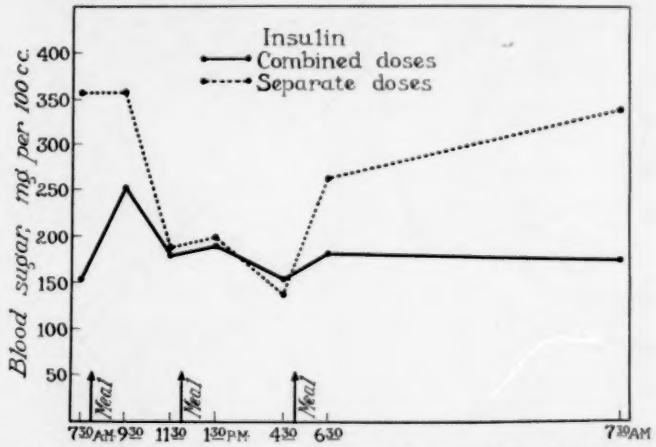

Chart 1 (case 1).—Comparison of mean curves obtained on administering the two types of insulin in one syringe (combined dose) and on administering each type at a separate site (separate dose).

Because the patient weighed 21 pounds (9.5 kg.) more than her ideal weight, a diet of only 40 per cent more than her basal caloric requirements was prescribed. On this diet her weight was maintained throughout the period of observations. During the period of preliminary study it was determined that her daily requirement of insulin was approximately 80 units.

Fifteen blood sugar curves were obtained in this case. During the first part of our study we obtained blood sugar curves after the administration of mixtures of protamine zinc insulin and unmodified insulin in various ratios as follows: 1:5, 1:4, 1:3, 1:2, 1:1, 2:5 and 2:3, in the order named. The patient then was allowed a few days of rest. In the second part of the study, blood sugar curves were obtained after the administration of mixtures of the protamine zinc insulin to unmodified insulin in the ratios of 1:0 (protamine zinc alone), 1:1, 1:2, 1:3 and 1:4, in that order. In the third part of our study we obtained blood sugar curves after the injection of protamine zinc and unmodified insulins in ratios of 1:1, 1:2 and 1:3 in separate sites. Finally a blood sugar curve was obtained after the administration of a suitable mixture one hour instead of half an hour before breakfast.

The "mean" curve calculated from the values for blood sugar in the various blood sugar curves obtained after the injection of mixtures of protamine zinc insulin and unmodified insulin in the ratios of 1:2, 1:3, 1:4, 2:3 and 2:5 is shown in chart 1. This curve shows the essential features of the pattern of blood sugar which resulted from the injection of mixtures representing what we may call "intermediate ratios." With one exception, satisfactory control of

the level of sugar in the blood was maintained throughout the twenty-four hours by the injection of these mixtures, that is, postprandial hyperglycemia was not excessive, and the fasting blood sugar levels were within the range of adequate control. The one exception to the good control was after the morning meal. All of the curves show this midmorning hyperglycemia, which presumably was due to a lag in the blood sugar–lowering effect of the mixtures. This finding coincides with the observation frequently made in cases in which the injection of the mixture fails to prevent hyperglycemia and heavy glycosuria at 11 a. m., even though both were under good control at 6 a. m. and 4 p. m. Ulrich observed this same phenomenon. Evidently, mixing the two insulins resulted in a lessening of the rapidity with which the unmodified insulin begins to exert its hypoglycemic effect. However, we do not believe that this slowing of the immediate hypoglycemic effect of the insulin in the mixtures constitutes a serious objection to their use, since the glycemic levels throughout most of the twenty-four hour period following the injection of the mixtures were within reasonable limits and the total excretion of dextrose was usually less than 20 Gm.

For comparison we have included in chart 1 a similar "mean" curve representing the mean values of blood sugar from three series of determinations obtained after the injection of the

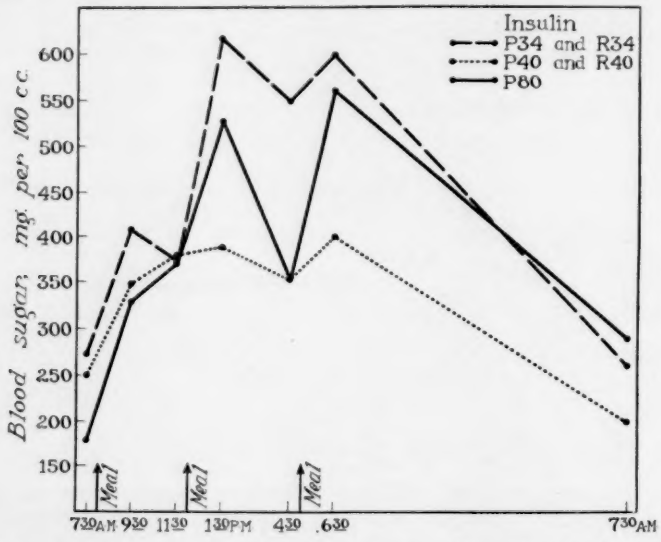

Chart 2 (case 1).—Comparison of blood sugar curves obtained after the administration of a total dose of protamine zinc insulin alone and mixtures of equal parts of the two types of insulin.

two insulins in separate sites. The ratios of the amounts of protamine zinc insulin and unmodified insulin represented in these curves were 1:1, 1:2 and 1:3. The second "mean" curve shows striking differences from the first "mean" curve, representing the effect of injection of the mixtures. It may be seen that the injection of the unmodified insulin in a separate site not only prevented the midmorning occurrence of hyperglycemia but also produced a rapid fall in the level of sugar in the blood shortly thereafter. However, during the latter part of the twenty-four hour curve the level of the blood sugar rose considerably higher than it did in the comparable period which followed the administration of the mixtures. This finding probably indicates that in the mixtures some of the unmodified insulin entered into combination with the excess protamine to form protamine insulin; thus the mixture contained relatively more protamine zinc insulin than would a similar total dose of insulin in which the protamine and unmodified components were given separately.

A curve of blood sugar obtained following the injection of the total dose as protamine zinc insulin alone is compared graphically in chart 2 with two curves obtained after the injection of mixtures of equal parts of protamine zinc and unmodified insulins. All three curves were similar; that is, with protamine zinc insulin alone or with a mixture of protamine zinc insulin

and unmodified insulin in the ratio of 1:1, control of the level of sugar in the blood was adequate in the fasting state but inadequate when the subject was allowed to eat. Marked postprandial hyperglycemia is characteristic of the effects of both types of insulin. Because of this similarity we believe that in mixtures of equal parts of protamine zinc and unmodified insulins the latter type of insulin must have entered for the most part into combination with the excess protamine, so that little unmodified insulin remains. It is obvious, therefore, that the patient gains little by the use of mixtures of equal parts of protamine zinc and unmodified insulins over the result from the use of the same total dose of protamine zinc insulin alone.

On comparison of the curve obtained after the injection of equal parts of the two types of insulin in a mixture and a curve obtained after the administration of a mixture of 1 part of protamine zinc insulin and 5 parts of unmodified insulin a marked difference is found (chart 3). Whereas little immediate hypoglycemic or unmodified insulin effect is evident in the first curve, in the second curve the rapid decrease in the level of sugar in the blood occurs after the administration of insulin. This result would be expected after the injection of a relatively large dose of unmodified insulin. We have interpreted this result to indicate that in a mixture in which the amount of unmodified insulin is much larger than the amount of protamine zinc insulin, only a small proportion of the unmodified insulin enters into combination with the extra protamine; an excess of unmodified insulin, therefore, is left to produce a marked immediate hypoglycemic effect. It should be noted, however, that despite the excess of unmodified insulin in this mixture the characteristic "lag" in hypoglycemic effect in the midmorning period is still evident. Perhaps the presence of the protamine modifies the activity of the unmodified insulin even though the two insulins in combination did not.

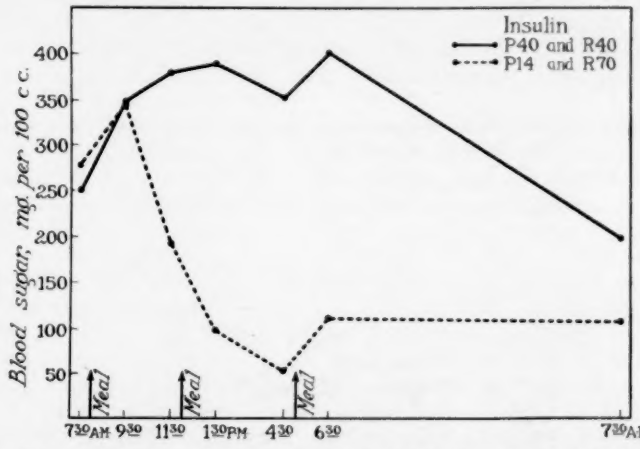

Chart 3 (case 1).—Comparison of curves obtained following injection of mixtures of insulin in which the ratio of protamine zinc insulin to unmodified insulin was either 1:1 or 1:5.

The "mean" curve representing the results of the injection of the two types in the various intermediate ratios half an hour before breakfast is compared with the results obtained after the administration of a suitable mixture one hour before breakfast in chart 4. We were interested in determining whether or not a more satisfactory control of the level of blood sugar could be obtained by giving the insulin long enough before the morning meal to eliminate the midmorning lag in blood sugar-lowering effect. As may be seen in chart 4, injecting the mixture earlier in the morning did eliminate the midmorning hyperglycemia, presumably because sufficient time elapsed between the injection of the insulin and the ingestion of food to permit the hypoglycemic effect of the insulin to begin before the ingestion of food started to elevate the blood sugar. However, in this case the remainder of the blood sugar curve obtained following this earlier injection did not show as smooth control of the glycemic level as did curves obtained following the injection of the insulin half an hour before breakfast.

Case 2.—Our second subject was an unmarried woman 21 years of age, whose diabetes had begun abruptly one year before her entry into the nutritional ward. During that time her diabetes had been well controlled by a standard diabetic diet and one daily injection of a mixture of protamine zinc and unmodified insulins.

On admission to the nutritional ward in January 1942 the patient weighed 122 pounds (55.5 Kg.) and was 66 inches (167 cm.) in height. General physical examination, examination of the ocular fundi and routine laboratory studies, including a roentgen study of the thorax and a flocculation test of the blood, revealed nothing of significance. Because her weight was approximately normal, a diet of 50 per cent more than her basal caloric requirements was

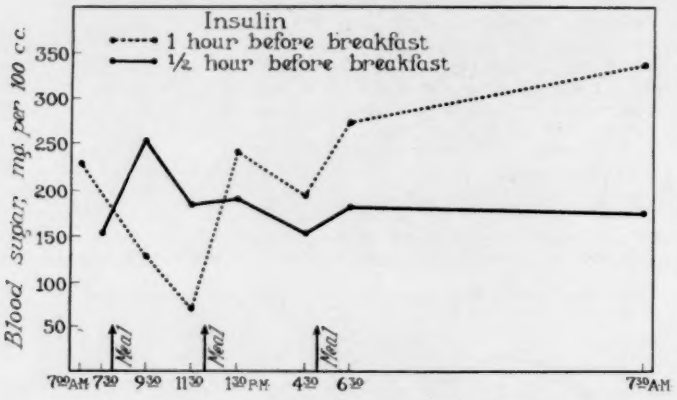

Chart 4 (case 1).—Comparison of blood sugar curves obtained after injecting mixtures of the two types of insulin one hour and half an hour before breakfast.

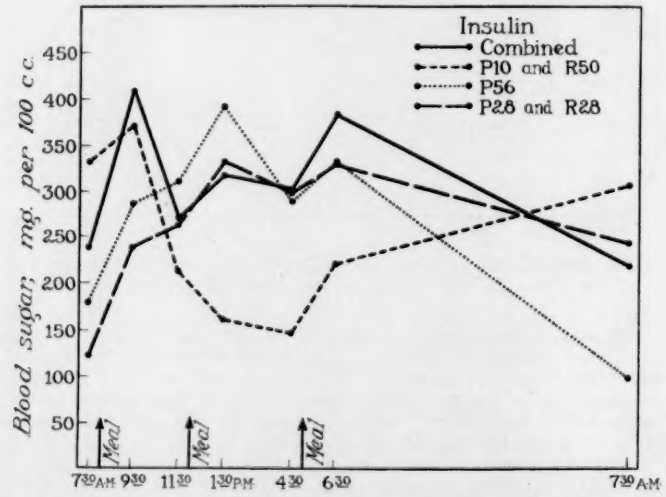

Chart 5 (case 2).—Six blood sugar curves. The curve labeled "combined" is the mean curve; the method of obtaining the mean curve and descriptions of the other curves are given in the text.

prescribed. During the first ten days of observation it was found that her daily insulin requirement was approximately 70 units.

Six blood sugar curves were obtained in this case. These are all represented in chart 2. The first curve is a "mean" curve calculated from three individual curves obtained after the injection of insulin mixtures in which the ratios of the protamine zinc insulin to the unmodified insulin were 1:2, 1:3 and 1:4, respectively. In nearly all respects, this mean curve of the level of sugar in the blood, in chart 2, is similar to the mean curve which we have already

presented for case 1. In this case, as in case 1, control of the level of sugar in the blood by the injection of various mixtures of the two types of insulin was good throughout most of the twenty-four hour period, with the exception of the period between the morning and noon meals.

The curves with dosage ratios of 1:1 and 1:0 in chart 5 indicate the similarity between an injection of a mixture of equal parts of protamine zinc and unmodified insulin and a single injection of protamine zinc insulin alone in effect on the blood sugar level throughout the twenty-four hours following their injection.

The curve in chart 5 with the ratio of 1:5 for the two types of insulin indicates that the injection of a mixture of insulins in this ratio produced the same effect on the level of sugar in the blood in case 2 as it did in case 1. This mixture of 5 parts of unmodified insulin to 1 part of protamine zinc insulin resulted in a predominantly rapid hypoglycemic or unmodified insulin effect.

COMMENT

Although our studies have been limited, we believe that our results so far warrant at least certain tentative deductions.

On the whole, mixtures of protamine zinc insulin and unmodified insulin have been shown to be capable of controlling to a satisfactory degree the levels of sugar in the blood of diabetic patients throughout the twenty-four hour period following their injection. With the exception of the period after breakfast, postprandial elevations of the blood sugar were minimal. We feel that the lag in the immediate hypoglycemic effect of the mixtures does not constitute a serious objection to their use in cases of severe diabetes.

We have not been able to demonstrate that any one ratio of the protamine zinc insulin to unmodified insulin gave an optimal effect in the 2 cases studied, nor were we able to find an ideal mixture in a study of ratios such as seemed to obtain in the 100 cases of diabetes in which the two insulins were given in a single injection. However, ratios of protamine zinc insulin to unmodified insulin which lay between the two extremes of 1:1 and 1:5 gave the most satisfactory control in most instances; that is, mixtures in which the ratios of protamine zinc insulin to unmodified insulin were 1:2, 1:3, 1:4, 2:3 and 2:5 were capable of adequate control of the blood sugar during the twenty-four hours after their injection. The use of a mixture of equal parts of the two insulins resulted in blood sugar curves very similar to those obtained when the dose consisted of protamine zinc insulin alone. In such a mixture, we believe, most of the unmodified insulin was in combination with the excess protamine. On the other hand, a mixture of 1 part of protamine zinc insulin to 5 parts of unmodified insulin resulted in a marked immediate hypoglycemic effect such as might be expected to follow the injection of a large dose of unmodified insulin alone. Evidently in such a mixture most of the unmodified insulin remained uncombined.

We did not find that injection of the two types of insulins at separate sites gave as satisfactory control of the blood sugar level in the subsequent twenty-four hours as their injection together. Following their injection in separate sites, a marked immediate hypoglycemic effect was obtained, but smooth control of the level of the blood sugar during the remainder of the day and especially overnight did not result.

Finally, we tried to eliminate the midmorning lag in hypoglycemic effect of the mixtures of the two insulins by injection of the dose of insulin one hour instead of half an hour before breakfast. Although this method eliminated the lag, it did not result in smoother control of the blood sugar during the remainder of the twenty-four hours.

Mayo Clinic.

IN SITU EFFECTS OF ANTACIDS IN DUODENAL ULCER

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An attempt at neutralization of the acid gastric juice is one of the basic purposes common to most of the conventional methods of treatment of peptic ulcer. In order to secure more effective neutralization it has become rather universal practice to employ any of several antacid medications, all of which have been extolled for their peculiar virtues and each of which has its own group of proponents. Alkaline substances continue to succeed one another in favor, largely as their several advocates are able to demonstrate a greater degree of reduction or a more prolonged reduction of acidity in the stomach.

The concerted efforts directed toward modification of gastric acidity are natural outgrowths of the emphasis which has been laid on the acid factor in ulcer. It is surprising, however, that so much attention has been given to gastric acidity when the vast majority of the ulcers encountered clinically are situated not in the stomach but in the first part of the duodenum. If acidity is really an important factor in duodenal ulcer, then the acidity and neutralizing ability at the actual site of the ulcer and not those in the stomach should be ascertained. Similarly, if antacid therapy is really beneficial in the management of duodenal ulcer because of reduction of acidity, then the changes produced by antacids in the acidity and neutralizing ability at the actual site of the ulcer rather than in the stomach should be determined.

Our purpose in this study was to observe the simultaneous effects of some of the commonly employed antacids on the reaction and neutralizing ability in the pyloric antrum and in the duodenal bulb in a group of patients with chronic duodenal ulcer. In our opinion, antacid therapy for duodenal ulcer can be properly evaluated from the standpoint of changes in acidity only by observations made directly at the locale of the ulcer—only by observations, in other words, of the in situ effects.

MATERIAL

A group of 17 patients (13 men and 4 women) ranging in age from 26 to 59 years were selected from the outpatient gastrointestinal disease clinic of the Jefferson Hospital. All of them either were complaining at the time of symptoms attributable to an ulcer or had been symptom free for a very short period. A number had had previous episodes of bleeding, and

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all of them had definite roentgenologic evidence of a nonobstructive duodenal ulcer. In the few instances in which it had been done, gastroscopic examination revealed an essentially normal gastric mucosa.

METHOD

Each patient appeared in the morning before breakfast and after a twelve hour fast. A specially constructed double lumen tube was employed also and a procedure followed which allowed more or less constant fluoroscopic control and also permitted the making of roentgenograms providing proof of the position of the tube.[1] Material was simultaneously aspirated from the pyloric antrum and from the duodenal cap at intervals of ten minutes. Specimens were collected for one-half hour while the subject was in the fasting state and for two hours after his ingestion of an Ewald meal, consisting of two pieces of dry toast or stale bread and 250 cc. of tap water. Immediately after the withdrawal of the specimens at the thirty minute postprandial interval each patient was given by mouth either 15 cc. of a preparation of aluminum hydroxide gel [2] plus 15 cc. of tap water or 10 grains (0.6 Gm.) of sodium bicarbonate and 30 grains (2 Gm.) of calcium carbonate (Sippy powder) plus 15 cc. of tap water.

The p_H of each specimen was determined at once by means of a Leeds-Northrup p_H indicator, which uses a glass electrode. After filtration the free and the total acidity of each specimen were estimated, with Töpfer's reagent and phenolphthalein as the respective color indicators.[3] For each duodenal specimen, in addition, there was determined what was called the excess neutralizing ability.[4] This is expressed as the amount of tenth-normal hydrochloric acid necessary to lower the p_H to the point at which Töpfer's reagent indicated a positive reaction for free acid.[3]

The patients were divided into two groups. One patient served as a subject in both groups, making a total of 9 patients in each. On one group (7 men and 2 women) 19 experiments were performed with aluminum hydroxide gel, while on the other 7 men and 2 women 19 experiments were performed with Sippy powder. The 38 experiments so performed involved 3,703 separate determinations. The latter included 1,003 readings of p_H, 1,084 estimations of free acid, 1,084 estimations of total acidity and 532 determinations of excess neutralizing ability of the duodenal contents. In expressing the results, the 4 readings made with the subject in the fasting state were averaged to give a single value.

RESULTS

In the accompanying figures (1 to 8 inclusive) there are shown the curves obtained by plotting the average values observed with the use of the antacids aluminum hydroxide gel and Sippy powder. The curves of the controls, which are presented for comparison, represent the average values obtained for a group of patients with duodenal ulcer who had been fed the same Ewald meal and studied in a similar fashion but had not received any antacid.[5] Included among the controls are 12 of the 17 patients who comprise the series receiving an antacid, an attempt purposely being made to obtain studies on as many of the control patients as possible in order to insure a fairer comparison. Of such patients, a few who had had active symptoms when the control observations were made were symptom free at the time of the experiments with the antacid. Inasmuch as our primary interest lay in observing the effects of orally administered alkaline

1. Berk, J. E.; Rehfuss, M. E., and Thomas, J. E.: A Method for the Simultaneous Aspiration of the Contents of the Stomach and the First Part of the Duodenum, J. A. M. A. **119**:259 (May 16) 1942.

2. The preparation used was amphojel (John Wyeth & Brother, Inc.).

3. Berk, J. E.; Thomas, J. E., and Rehfuss, M. E.: Limitations in the Use of Color Indicator in Gastric Analysis, Am. J. Digest. Dis. **9**:106, 1942.

4. Berk, J. E.; Thomas, J. E., and Rehfuss, M. E.: (*a*) The Reaction and Neutralizing Ability of the Contents of the Pyloric Antrum and First Part of the Duodenum in Normal Dogs Following an Ewald Meal, Am. J. Physiol. **136**:157, 1942; (*b*) footnote 3.

5. Berk, J. E.; Rehfuss, M. E., and Thomas, J. E.: The Effect of Ulcer on the Reaction and Neutralizing Ability in the Duodenal Bulb, Arch. Int. Med. **70**:959 (Dec.) 1942.

substances on gastric and duodenal acidity, we did not feel that the subsidence of active symptoms in these patients impaired the validity of the comparisons of acidities determined before and after ingestion of an antacid, because it has been fairly well established that no essential change occurs in the degree of gastric acidity with healing of a duodenal ulcer.[6] The close adherence of the control and the antacid curves to each other in the period prior to the administration of the respective antacids (figs. 1, 3, 5 and 7) may be taken as support for this assumption.

Acidity in p_H Units (figs 1 and 2).—Stomach: The two antacids caused decreases in average hydrogen ion concentration of equal duration, although the magnitude of the decrease was greater with Sippy powder than with aluminum

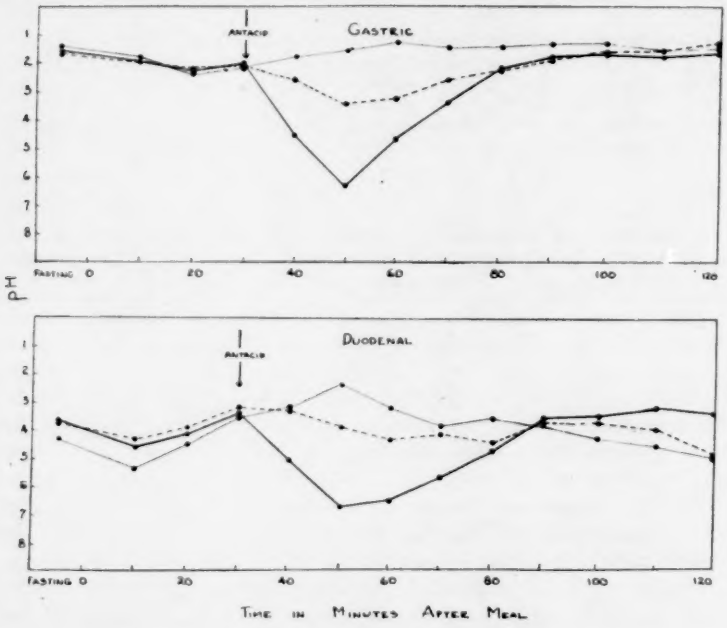

Fig. 1.—Average acidity in p_H units of samples collected simultaneously from just above and just below the pylorus before and after the administration of an antacid. The dotted line represents values for patients who received aluminum hydroxide gel; the heavy unbroken line, for patients who received Sippy powder, and the light unbroken line, for patients who did not receive an antacid (controls).

6. (*a*) Bloomfield, A. L., and French, L. R.: Basal Gastric Secretion in Cases of Peptic Ulcer: Relation of Acidity to Healing of Ulcer, J. Clin. Investigation **17**:667, 1938. (*b*) Bockus, H. L.; Glassmire, C., and Bank, J.: Fractional Gastric Analysis in Two Hundred Cases of Duodenal Ulcer, Am. J. Surg. **12**:6, 1931. (*c*) Brown, C. F. G., and Dolkart, R. E.: Gastric Acid During Recurrences and Remissions of Duodenal Ulcer, Arch. Int. Med. **60**:680 (Oct.) 1937. (*d*) Hurst, A. F., and Venables, J. F.: The True Incidence of Hyperchlorhydria in Gastric and Duodenal Ulcer, Guy's Hosp. Rep. **79**:249, 1929. (*e*) Sandweiss, D. J.; Sugarman, M. H.; Friedman, M. H. F.; Saltzstein, H. C., and Farbman, A. A.: The Effect of Urine Extracts on Peptic Ulcer: An Experimental and Clinical Study, Am. J. Digest. Dis. **8**:371, 1941.

hydroxide gel. Neither antacid, however, was eminently successful in causing any prolonged elevation of average p_H above 3.5, the value which we had adopted as the critical one for free acid.[3] With Sippy powder the forty, fifty and sixty minute determinations were in excess of p_H 3.5 and hence negative for free acid; with aluminum hydroxide gel only the fifty minute determination exceeded this value (fig. 1).

The contrast in effects on gastric hydrogen ion concentration was more favorably seen in the frequency distribution of the observations made in the period after administration of the antacid (fig. 2). Not one of the control values exceeded p_H 3.5; in fact all of them were p_H 3.0 or less. On the other hand, 10.1 per cent of the readings following ingestion of aluminum hydroxide gel and 31.1 per cent of those following ingestion of Sippy powder were greater than p_H 3.5.

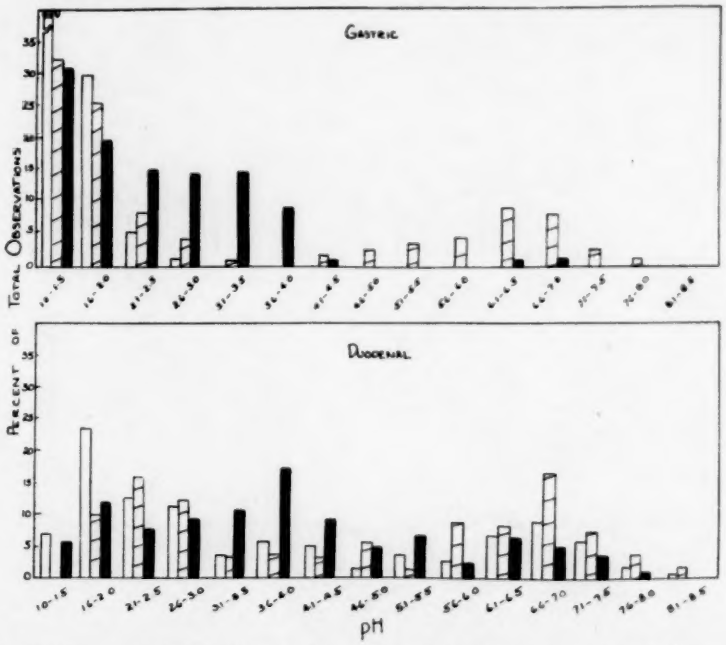

Fig. 2.—Frequency distribution of observations of p_H of samples collected simultaneously from just above and just below the pylorus after the administration of an antacid and in control experiments during the corresponding period. Values for patients receiving aluminum hydroxide gel are represented by solid bars; for patients receiving Sippy powder by bars with cross hatching, and for patients not receiving an antacid, by white bars.

No secondary rise in gastric hydrogen ion concentration occurred with either antacid during the period of observation.

Duodenum: The control patients displayed an ineffective neutralizing ability in their duodenal bulbs at the forty, fifty and sixty minute readings (inability to neutralize gastric free acid as evidenced by an inability to maintain a p_H of 3.5 or greater). Aluminum hydroxide gel corrected this defect to some extent, in that only the forty minute determination showed ineffective neutralization; otherwise, the

general effect on duodenal p_H was slight. Sippy powder acted more promptly and produced a higher peak level of average duodenal p_H; this was largely offset, however, by a secondary increase in hydrogen ion concentration, which was so great that ineffective neutralization (p_H of 3.5 or less) characterized the last half-hour of the observation period (fig. 1).

The general ineffectiveness of these antacids in the duodenum is well shown in the frequency distribution of the observations (fig. 2). The contents of the first part of the duodenum in the specially noted postantacid phase contained free acid (p_H 3.5 or less) in 57.7 per cent of the control observations and in 40.6 per cent of the observations following use of Sippy powder and in 43.4 per cent of those following use of aluminum hydroxide gel—differences of questionable significance.

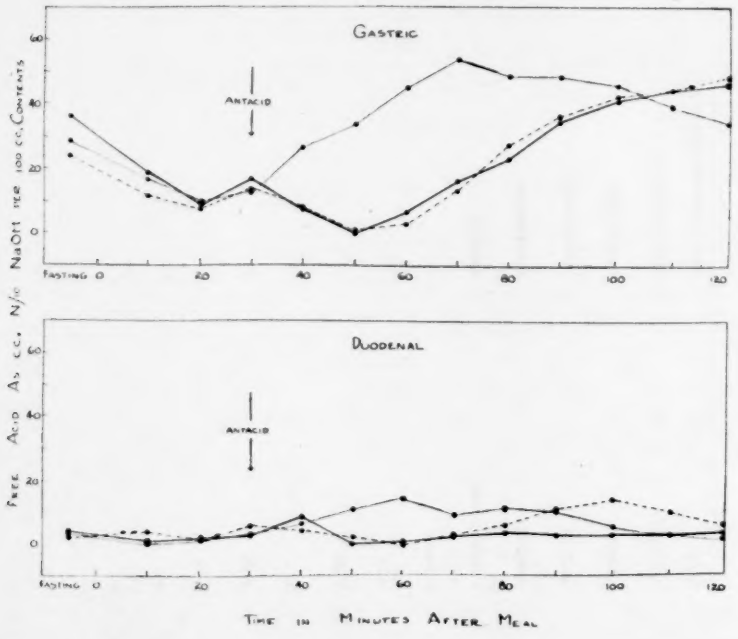

Fig. 3.—Average free acid as determined on samples collected simultaneously from just above and just below the pylorus before and after the administration of an antacid. See the legend for figure 1 for an explanation of the curves.

The graphic average curves of p_H in the stomach and duodenum following administration of an antacid bore a rough resemblance to each other. An exact parallelism, however, was not discerned, and in the last half-hour of the observation period the duodenal curves were distinctly of different pattern than their respective gastric homologues (fig. 1). Of special note, too, was the exhibition of a secondary rise in duodenal acidity with Sippy powder in the absence of such a phenomenon in the stomach. These discrepancies are worthy of emphasis, for they illustrate an inability to accept observations of gastric behavior as accurate indexes of the corresponding effects on acidity in the first part of the duodenum.

Free Acid (figs. 3 and 4).—Stomach: Even though a complete achlorhydria was obtained at a single interval reading only (fifty minutes), a diminution of the average values of free acid in the gastric juice was obtained. This was of about equal magnitude and duration with the two antacids (fig. 3). All of the control specimens contained some titratable free acid, whereas 37 per cent of the specimens studied after ingestion of Sippy powder and 35.3 per cent of those examined after ingestion of aluminum hydroxide gel were colorimetrically negative for free acid. Both these percentages are greater than was indicated by the corresponding gastric p_H values (fig. 2). This is not surprising, however, for, as we have pointed out,[3] with our technic the filtration and dilution of the specimens preparatory to colorimetric titration result in a number of false negative readings for free acid. Since

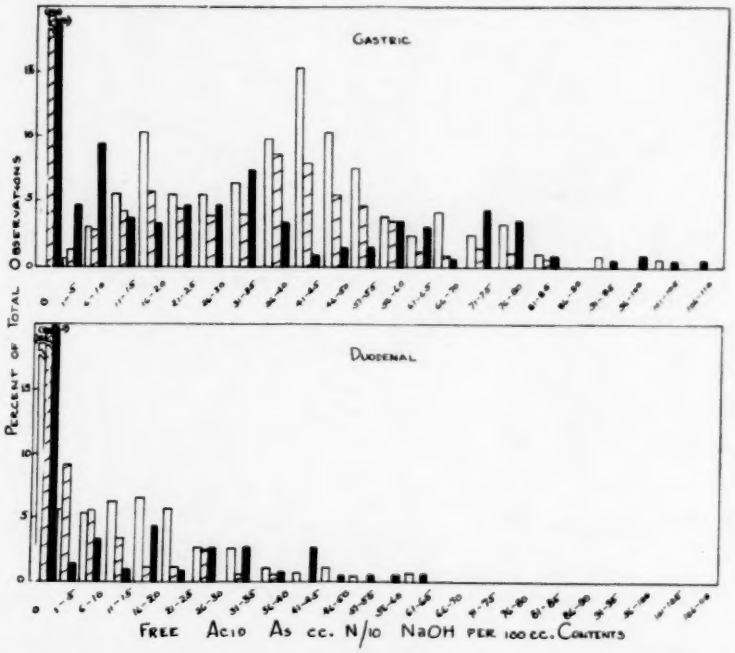

Fig. 4.—Frequency distribution of observations of free acid as determined on samples collected simultaneously from just above and just below the pylorus after the administration of an antacid and in control experiments during the corresponding period. See the legend for figure 2 for an explanation of the figure.

our average end point with Töpfer's reagent was close to p_H 3.5,[3] all specimens whose p_H in the unfiltered, undiluted state is 3.5 or less must be considered as containing free acid. Interpreted in the light of this criterion, the p_H values afford the more accurate index of the true incidence of achlorhydria.

A mild secondary rise in average gastric free acid was seen following use of each antacid (fig. 3), a phenomenon which was not observed in the behavior of the average gastric p_H.

The graphic curve of average gastric free acid after ingestion of aluminum hydroxide gel (fig. 3) adopted a definitely different pattern than that shown by the

corresponding curve of average duodenal p_H (fig. 1). It may be said, then, that this measure of acidity in the stomach, as far as aluminum hydroxide gel is concerned at any rate, cannot be taken to indicate with any surety the coexistent effective acidity (p_H) in the duodenal bulb.

Duodenum: Despite its salutary effect on gastric free acid, aluminum hydroxide gel failed to display an ability to reduce duodenal free acid in a similar fashion. Not only was it less effective in this respect than was Sippy powder, but it produced a secondary rise in duodenal acidity which did not occur after use of Sippy powder (fig. 3). A more favorable comparison appears when the percentage of samples taken after ingestion of an antacid that are colorimetrically negative for free acid is considered; 76.2 per cent of the observations after use of aluminum

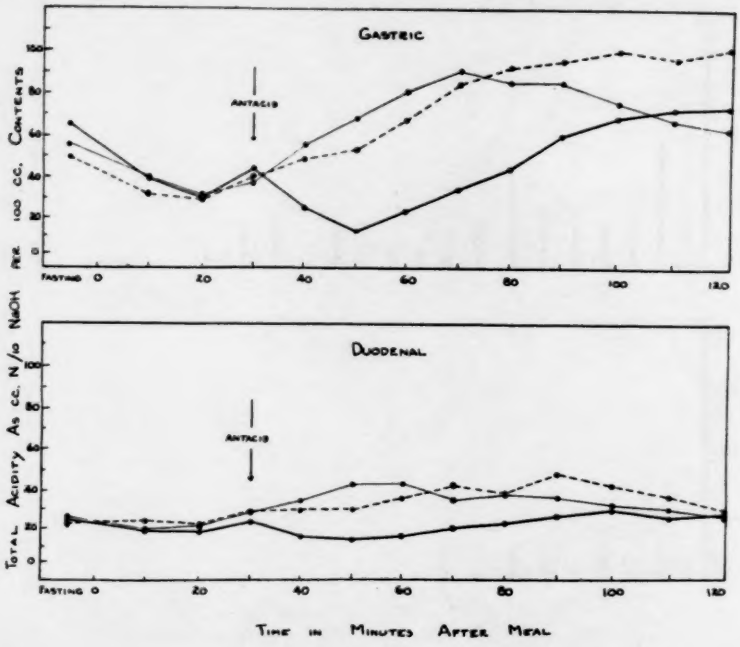

Fig. 5.—Average total acidity of samples collected simultaneously from just above and just below the pylorus before and after the administration of an antacid. See the legend for figure 1.

hydroxide gel and 75.5 per cent of those after use of Sippy powder showed no free acid, in contradistinction to 57.7 per cent of the control observations (fig. 4). These percentages, however, are again greater than the corresponding ones based on determinations of duodenal p_H and must be interpreted in the light of the error which is known to exist in the method of colorimetric titration.

Total Acidity (figs. 5 and 6).—Stomach: Aluminum hydroxide gel not only appeared to be devoid of any beneficial effect on average gastric total acidity but, paradoxically, caused a greater concentration of titratable acidity than that which obtained without use of any antacid (fig. 5). This situation, however, is more apparent than real, for it is to be remembered that the sodium hydroxide used in

the titrimetric procedure combined not only with the hydrochloric acid of the gastric contents but with the aluminum chloride formed from the interaction of the aluminum hydroxide of the gel and the hydrochloric acid of the chyme. Therefore, determinations of total acidity following the administration of aluminum hydroxide gel give no indication of its efficacy as an antacid.

Sippy powder exhibited an effect on gastric average total acidity similar to that on free acid (fig. 3). The effect reached its peak rapidly, progressively lessened and finally reached the control level after about an hour. The comparatively lesser action of this antacid on the p_H in the duodenal cap (fig. 1) bespeaks the fact that measurement of gastric total acidity also fails as a reliable index of the actual changes in effective duodenal acidity (p_H) which may follow the use of an antacid.

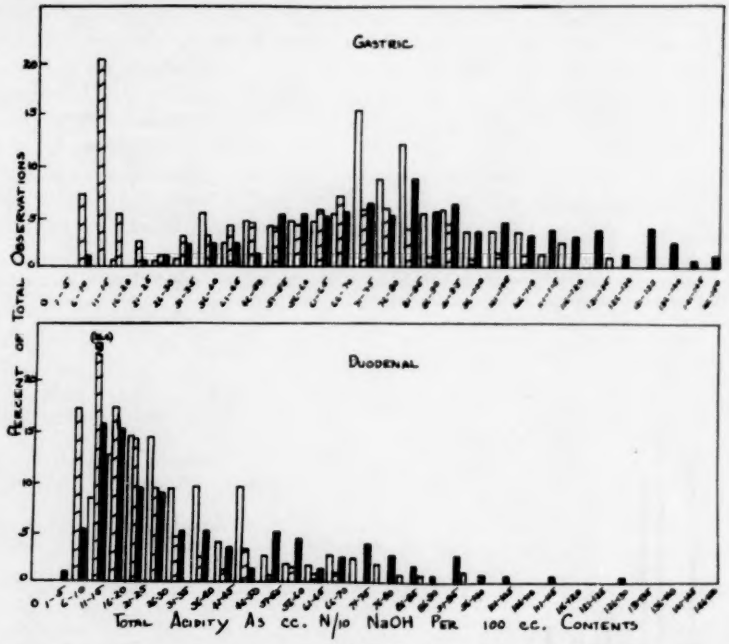

Fig. 6.—Frequency distribution of observations of total acidity of samples collected simultaneously from just above and just below the pylorus after the administration of an antacid and in control experiments during the corresponding period. See the legend for figure 2.

Duodenum: As in the stomach and for the reasons stated in that connection, aluminum hydroxide gel appeared to contribute little if at all to lowering the average total acidity of the contents of the duodenal cap (fig. 5). Sippy powder, on the other hand, effected a reduction of total acidity in this area.

Excess Neutralizing Ability of the Duodenal Contents (figs. 7 and 8).—Excess neutralizing ability has been defined [4] as a measure of the reserve capacity possessed by the contents of the duodenal bulb to neutralize, buffer and dilute the chyme received from the stomach above that necessary to offset the free acid content. Aluminum hydroxide gel, it will be seen in figure 7, was essentially non-

contributory to this reserve ability. Sippy powder, on the contrary, greatly enhanced the excess neutralizing ability of the duodenal contents. The latter action may be attributed, in all probability, to the free sodium bicarbonate carried over into the duodenum along with the chyme emptying from the stomach. As with the other observed effects of Sippy powder, the enhancement was of relatively brief duration and was offset in the terminal phase by a diminution of the reserve capacity below that of the control series.

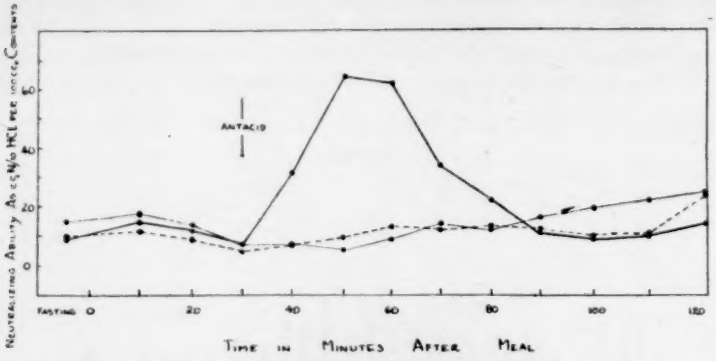

Fig. 7.—Average excess neutralizing ability of the duodenal contents before and after the administration of an antacid. See the legend for figure 2.

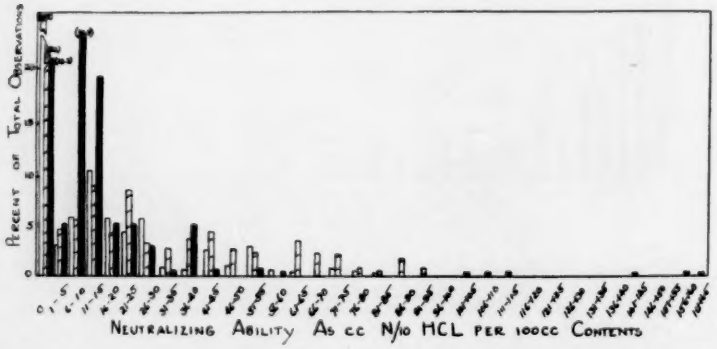

Fig. 8.—Frequency distribution of observations of excess neutralizing ability of the duodenal contents after the administration of an antacid and in control experiments during the corresponding period. See the legend for figure 2.

COMMENT

In presenting the results, attention repeatedly has been called to the disparity between the observed simultaneous gastric and duodenal effects of the two antacids. It was noted that salutary effects on gastric acidity were commonly associated with comparative ineffectiveness as regards reduction of duodenal acidity and that undesirable secondary rises in acidity occurred in the duodenum in the absence of

such phenomena in the stomach. It may be concluded, therefore, that the in situ effects of antacids on duodenal acidity in patients with duodenal ulcer cannot be predicted from their behavior in the stomach, just as their intragastric effects, in turn, cannot be predicted from their potential in vitro neutralizing capacity.[7]

The effective acidity in the first part of the duodenum, the harboring nest of most clinical ulcers, is determined by the hydrogen ion concentration of its contents, which in turn finds expression in the p_H value. A lack of close correlation was pointed out between the values of the several measures of gastric acidity and the coexistent p_H in the duodenal cap. It is important to emphasize the fact that, generally speaking, after the use of an antacid none of the customary indexes of gastric acidity may be taken to indicate reliably the coexistent effective acidity (p_H) in the duodenal bulb.

The results indicate that the oral administration of an antacid in the commonly employed therapeutic doses enhances the neutralizing ability of the contents of the first part of the duodenum. It is to be stressed, however, that the reduction of intraduodenal acidity was not great, lasted only a comparatively short period of time and was followed in the instance of Sippy powder by a rebound increase in duodenal hydrogen ion concentration. The use of larger amounts and/or more frequent doses of antacid might well overcome these shortcomings, but the patient with an ulcer would then become subjected to the added risk of such complications as alkalosis,[8] impaired renal function with kidney stone formation,[9] constipation,[10] fecal impaction,[8] intestinal obstruction[11] and interference with absorption of inorganic phosphates.[12] We have found that duodenal acidity is greatly affected by the type of food undergoing digestion [13] and that in dogs fats (cream, olive oil and

7. (*a*) Breuhaus, H. C., and Eyerly, J. B.: Antacids: Their Effect by Titration and Within the Human Stomach, Ann. Int. Med. **14**:2285, 1941. (*b*) Eyerly, J. B.: Comparative p_H Values Within the Stomach, Pylorus, and Duodenum in Antacid Therapy, Am. J. Digest. Dis. **7**:431, 1940.

8. (*a*) Dick, C. F., and Eisele, C. W.: The Treatment of Peptic Ulcer Without Alkalis, J. A. M. A. **118**:38 (Jan. 3) 1942. (*b*) Eisele, C. W.: Changes in the Acid-Base Balance During Alkali Treatment for Peptic Ulcer, Arch. Int. Med. **63**:1048 (June) 1939. (*c*) Hardt, L. L., and Rivers, A. B.: Toxic Manifestations Following the Alkaline Treatment of Peptic Ulcer, ibid. **31**:171 (Feb.) 1923. (*d*) Kirsner, J. B., and Palmer, W. L.: The Role of Chlorides in Alkalosis Following the Administration of Calcium Carbonate, J. A. M. A. **116**:384 (Feb. 1) 1941.

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12. Fauley, G. B.: Freeman, S.; Ivy, A. C.; Atkinson, A. J., and Wigodsky, H. S.: Aluminum Phosphate in the Therapy of Peptic Ulcer: Effect of Aluminum Hydroxide on Phosphate Absorption, Arch. Int. Med. **67**:563 (March) 1941. Freeman, S., and Freeman, W. M.: The Interference in the Absorption of Inorganic Phosphorus by Aluminum Hydroxide: Its Use in Children with Chronic Renal Insufficiency, Am. J. Physiol. **133**:281, 1941. Street, H. R., and Barlow, O. W.: The Relative Effects of Aluminum Hydroxide and Aluminum Sulfate on the Absorption of Dietary Phosphorus by the Rat, ibid. **133**:465, 1941.

13. Berk, J. E.; Thomas, J. E., and Rehfuss, M. E.: (*a*) The Effect of Gastric Hypersecretion on the Reaction and Neutralizing Ability of the Contents of the First Part of the Duodenum in Normal Dogs, Am. J. Digest. Dis. **9**:297, 1942; (*b*) The Effect of a Cream Meal on the Acidity and Neutralizing Ability of the Contents of the Duodenal Bulb in Normal Dogs, Am. J. Physiol. **136**:285, 1942; (*c*) footnote 4 *a*. (*d*) Thomas, J. E.: The Maximal Acidity of the Intestinal Contents During Digestion, Am. J. Digest. Dis. **7**:195, 1940. (*e*) Thomas, J. E., and Crider, J. O.: The Effect of Fat on the p_H of the Contents of the Duodenum, Am. J. Physiol. **114**:603, 1936.

beef fat) exhibit a striking depressant effect on duodenal acidity which is maintained for a considerable time.[13c,e] True, the amounts of fat we employed were greatly in excess of the amounts which are commonly given to patients; yet there is evidence that small doses of fat (olive oil and cod liver oil) depress secretion in the gastric pouch in dogs effectively and over long periods.[14] One might therefore expect a similarly effective action in the duodenum from small doses of such palatable fats as cream. Certainly the use of fats is devoid of the inconvenience, expense and complications attendant on the frequent administration of antacid medications. Should a duodenal antacid effect prove desirable in the management of a patient with ulcer, the preferential use of dietary measures, especially of fatty foodstuffs, is to be strongly considered.

Accumulated clinical experience leaves no doubt that antacid medications exert a beneficial action in the treatment of patients with duodenal ulcer. Basically the reason for their use and the enthusiasm with which they have been applied in the therapy of ulcer stem from the importance which has been assigned to the acid factor in this disease and to the assumed need for its modification. The literature, however, is replete with reports denying any remarkable or sustained neutralizing effects in the stomach following ingestion of an antacid.[15] Our results indicate, further, absence of any pronounced or prolonged neutralization at the site of the duodenal ulcer when a single therapeutic dose of an antacid is given to a patient with ulcer after an Ewald meal. In our own experience as well as in that of others,[8a] most patients with uncomplicated duodenal ulcer respond equally satisfactorily on a regimen devoid of antacids as when antacids are employed. The disappearance of abdominal pain after the ingestion of an antacid may alone warrant its employment, in spite of the demonstrated lack of any correlation with the changes in gastric acidity.[15k]

The most arresting evidence striking at the very foundation of the popular theory of antacid therapy is the demonstration that definite healing of experimental (Mann-Williamson) ulcers in dogs and distinct symptomatic improvement in patients with duodenal ulcer may occur with the use of extracts from the urine of pregnant and of normal women without any decrease in the gastric secretory response to stimuli.[6e] It is difficult to escape the conclusion, therefore, that what-

14. Komarov, O., and Komarov, S. A.: The Effect of Olive Oil and Cod-Liver Oil on Gastric Secretion in the Dog, Canad. M. A. J. **43**:129, 1940.

15. (*a*) Adams, W. L.; Einsel, I. H., and Meyers, V. C.: Aluminum Hydroxide as an Antacid in Peptic Ulcer, Am. J. Digest. Dis. **3**:112, 1936. (*b*) Boyd, T. E.: The Influence of Alkalies on the Secretion and Composition of Gastric Juice: I. The Effect of the Prolonged Administration of Sodium Bicarbonate and Calcium Carbonate, Am. J. Physiol. **71**: 455, 1925. (*c*) Breuhaus and Eyerly.[7a] (*d*) Brown and Dolkart.[6c] (*e*) Crohn, B. B.: Studies in Fractional Estimation of Gastric Contents: II. Effects of Antacid Medication on Gastric Acidity and Secretion, Am. J. M. Sc. **155**:801, 1918. (*f*) Degener, M.: Untersuchungen über den Einfluss von Alkalien auf Motilität und Sekretion des Magens mittels der fraktionierten Ausheberung, München. med. Wchnschr. **75**:1838, 1928. (*g*) Eyerly.[7b] (*h*) Ivy, A. C.; Terry, L.; Fauley, G. B., and Bradley, W. B.: The Effect of Administration of Aluminum Preparations on the Secretory Activity and Gastric Acidity of the Normal Stomach, Am. J. Digest. Dis. **3**:879, 1936. (*i*) Kirsner, J. B.: A Further Study of the Effect of Various Antacids on the Hydrogen Ion Concentration of the Gastric Contents, ibid. **8**:53, 1941. (*j*) Kirsner, J. B., and Palmer, W. L.: The Effect of Various Antacids on the Hydrogen Ion Concentration of the Gastric Contents, ibid. **7**:85, 1940. (*k*) Steigmann, F., and Fantus, B.: Acidity Modification Therapy in Peptic Ulcer, ibid. **7**:197, 1940. (*l*) Wosika, P. H., and Emery, E. S., Jr.: The Effectiveness of the Sippy Regimen in Neutralizing the Gastric Juice of Patients if the Amount of Alkali Is Not Varied, Ann. Int. Med. **9**:1070, 1936. (*m*) Wylkie, D.: The Influence of Certain Antacids on the Acidity of Human Gastric Juice, with Special Reference to Magnesium Trisilicate, Edinburgh M. J. **47**:336, 1940.

ever is the contribution of antacids to the management of patients with duodenal ulcer, their beneficial clinical action must be attributed to something more than their slight efficaciousness in reducing acidity at the site of the ulcer.

A comparative evaluation of the relative merits of the two antacids employed was not a primary purpose in this study. In many respects Sippy powder showed a neutralizing ability superior to that of aluminum hydroxide gel; but this seeming excellence requires qualification, and the suggested superiority must be accepted with caution. Aluminum hydroxide gel is known to be a slow acting antacid. With our method of study the withdrawal of small amounts of gastric and duodenal contents at ten minute intervals, all of which must have contained some of the administered antacid, would affect the end results of a slower acting antacid to a much greater degree than it would such a rapid acting one as Sippy powder. Despite a prompter and more rapid decrease in duodenal hydrogen ion concentration after ingestion of Sippy powder, there followed a secondary rise which tended to offset the apparent advantage of Sippy powder over aluminum hydroxide gel.

SUMMARY AND CONCLUSIONS

The in situ effects of antacids on duodenal acidity in patients with duodenal ulcer cannot be predicted from their behavior in the stomach.

After the ingestion of an antacid by a patient with duodenal ulcer none of the customary indexes of gastric acidity may be taken to indicate reliably the coexistent effective acidity (p_H) in the duodenal bulb.

Oral administration of an antacid in the usual therapeutic dose to a patient with duodenal ulcer does reduce the acidity of the contents of the first part of the duodenum. The reduction of intraduodenal acidity, however, is neither great nor long lasting and may be followed by a rebound increase.

The beneficial clinical action of antacids in the management of patients with duodenal ulcer must be attributed to something more than their slight efficaciousness in reducing acidity at the site of the ulcer.

Dr. B. B. Vincent Lyon gave us permission to use the patients and facilities of the gastrointestinal disease clinic, and Drs. Melvin Dillman and Karl Kornblum performed the roentgen studies on each subject.

SYMPTOMS AND INCIDENCE OF ANEMIA IN HERNIA AT THE ESOPHAGEAL HIATUS

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Instances of true hernia at the esophageal hiatus were recorded not infrequently in the literature of the early part of this century, but, with improvement in roentgenographic technic during the past twenty years and with accumulating interest in the subject, the rather high incidence of the condition has been recognized. The incidence in relation to the number of gastrointestinal roentgen studies made by several authors has varied from 0.75 to as high as 2.9 per cent of the series.[1] This must not be interpreted as evidence that such a high percentage of the general population has hiatal hernia, because the majority of the roentgen examinations were made for persons with complaints referable to the gastrointestinal tract.

Åkerlund[2] in 1926 cited 60 cases recorded in the literature up to that time and reported 24 of his own. Harrington[3] reported 680 cases seen at the Mayo Clinic between Jan. 1, 1908 and Dec. 31, 1939. The first of these cases was diagnosed in 1908, at the time of an operation, and in 1921 the first diagnosis by roentgen examination was recorded.

Three varieties of so-called hiatal hernia have been described by Åkerlund:[2] that associated with a congenitally short esophagus, a paraesophageal type and a gastroesophageal type. In the type occurring with a congenitally short esophagus a part or all of the stomach is permanently within the thorax (partial or complete thoracic stomach). Failure of the esophagus to reach a proper length during development has made it impossible for the stomach to develop in the normal position, which is entirely within the peritoneal cavity. In the paraesophageal type of hiatal hernia the esophagus is of normal length and its lower end remains situated below the level of the diaphragm in its normal position whereas the fundus of the stomach is herniated through the esophageal hiatus so that it lies within the posterior mediastinum. In the gastroesophageal type the esophagus is of normal length, but the lower end is carried up above the level of the diaphragm with the herniated stomach, which lies in the posterior mediastinum.

Harrington[3] expressed the opinion that in some instances the stomach is drawn into the thorax by cicatricial contraction of a healed ulcer at the lower end of the esophagus, the resulting condition being confused with hernia of the

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From the Medical Clinic of the Peter Bent Brigham Hospital.

1. (*a*) Ritvo, M.: Hernia of the Stomach Through the Esophageal Orifice of the Diaphragm, J. A. M. A. **94**:15 (Jan. 4) 1930. (*b*) Eisen, D.: Esophageal Hiatus Hernia, Canad. M. A. J. **39**:207 (Sept.) 1938. (*c*) Rigler, L. G., and Eneboe, J. B.: The Incidence of Hiatus Hernia in Pregnant Women and Its Significance, J. Thoracic Surg. **4**:262 (Feb.) 1935. (*d*) Levy, M. D., and Duggan, L. B.: Hiatus Hernia of the Stomach, South. M. J. **34**:351 (April) 1941.

2. Åkerlund, A.: Hernia diaphragmatica hiatus oesophagei vom anatomischen und röntgenologischen Gesichtspunkt, Acta radiol. **6**:3, 1926.

3. Harrington, S. W.: Diagnosis and Treatment of Various Types of Diaphragmatic Hernia, Am. J. Surg. **50**:381 (Nov.) 1940.

congenital variety. Dunhill [4] described in place of the third type what he termed "hernia diaphragmatica transversa." In this condition the esophagus is of normal length but the anatomic hiatus is replaced by a large defect due to nondevelopment of the crura of the diaphragm.

The presence of hiatal hernia is still commonly first suspected only after its demonstration by the roentgenologist. The symptoms presented by the patient are most likely to be ascribed to some disturbance such as peptic ulcer or carcinoma or disease of the gallbladder or of the organs within the thorax, the symptoms of which are more familiar to the physician. Attention may be directed away from the hernia as the cause of the symptoms because of the coexistence of one of those conditions and the hernia. The common failure of the physician to include hiatal hernia in the differential diagnosis is probably the result of variation in the symptom complex and of lack of knowledge of what the various symptoms are. Harrington [3] has referred to hiatal hernia as the "masquerader of the upper abdomen" because of the change in the symptom complex as the size and the condition of the hernia change with age.

The objects of the study reported here are two: (1) to determine those symptoms occurring in patients with herniation which may lead one to suspect the diagnosis; (2) to record the frequency of anemia in patients with hiatal hernia and its importance as a diagnostic aid.

MATERIAL STUDIED

The data recorded are based on 72 case histories of patients with hiatal hernia, taken from the wards and outpatient department of the Peter Bent Brigham Hospital and the private records of one of us (W. P. M.). Hernia of the type occurring with a congenitally short esophagus was present in 7 instances. Although there is some question as to whether or not this is true herniation because of the fact that the end of the esophagus and the stomach have never been in their normal position, these cases are most conveniently included for discussion with those of true hernia. The remaining 65 cases of hiatal hernia have not been further classified, because the data available did not warrant differentiation into smaller subgroups. It seemed to us likely that the distinction between the paraesophageal and the gastroesophageal type is largely dependent on the degree of herniation at the time the roentgen examination is made. The position of the lower end of the esophagus and the size of the portion of the stomach herniated into the posterior mediastinum depend largely on the condition of the patient at the time of examination.

Sex.—Of the 72 patients, 11 were men and 61 women. Eleven women were unmarried; 12 were married but had borne no children, and the marital status of 1 is unknown. The remaining 37 women had borne one or more children.

It has been generally recognized that hiatal hernia is more common in female than in male patients, as in our series. In the series of Rigler and Eneboe [1c] there were 15 females to 4 males. These authors also called attention to the frequency with which herniation accompanies pregnancy. They found roentgen evidence of hiatal hernia in 18.1 per cent of 116 multipara. Marks [5] observed that herniation occurred most commonly in women who are over 40 years of age and overweight.

Age.—The 72 patients were distributed with respect to decades of life at the time the diagnosis was made as follows: 30 to 39 years, 4; 40 to 49 years, 12; 50 to 59 years, 23; 60 to 69 years, 19; 70 to 79 years, 14. The youngest patient, a woman, was 33 years of age when the diagnosis was made, but the symptoms had persisted since a fall from a stone fence at the age of 20, when she landed prone with a large boulder under her abdomen. The oldest patient was 78. The average age of the series was 60 years. It was often difficult to determine the age at which the onset of symptoms occurred because of uncertainty as to whether these were the result of hernia or of some other ailment. However, as nearly as could be determined, the average age at onset of symptoms was 57 years.

4. Dunhill, T.: Diaphragmatic Hernia, Brit. J. Surg. **22**:475 (Jan.) 1935.

5. Marks, J. H.: Diaphragmatic Hernia and Associated Conditions, Am. J. Roentgenol. **37**:613 (May) 1937.

Harrington [6] found hiatal hernia to be most common in the decade between 50 and 60 years. Moersch [7] and also Levy and Duggan [1d] found the average age to be 55 years; the extremes in their series of 26 cases were 27 and 79 years. The average age of 128 patients with hiatal hernia reported by Jones [8] was 55 years. It is not clear whether the ages reported for these various series are those at the time of onset of symptoms or those at the time the diagnosis was made.

CONGENITALLY SHORT ESOPHAGUS AND THORACIC STOMACH

Bailey [9] was probably the first to direct attention to, and describe, a case of congenitally short esophagus with complete thoracic stomach when in 1919 he reported such a condition found during the dissection of the body of a 77 year old man. LeWald [10] was perhaps the first to recognize thoracic stomach by roentgen examination. In 1924 he described this condition in 2 persons, a child of 7 years and a man of 69 years. He stated that "thoracic stomach is an entity of congenital origin with development of the diaphragm below it, without structural defect." Truesdale [11] found reports of 20 cases of "complete thoracic stomach" and of 41 cases of "partial thoracic stomach" with a short esophagus in the literature up to 1935.

Seven of our series of patients with hiatal hernia were found to have a congenitally short esophagus. In only 1 of them was the stomach completely above the diaphragm—complete thoracic stomach. Five women and 2 men, 1 of whom also had pernicious anemia, comprise this group. A brief history of each of them is included here because of the somewhat unusual interest in this condition.

CASE 1.—A 59 year old woman, single, had for eighteen months previous to examination complained of regurgitation of food recently eaten and of having several times vomited bloody material. She also complained of heartburn, gas and distention in the upper part of the abdomen, as well as of the sensation that food met an obstruction half way down, and she seemed to have difficulty in swallowing solid foods. Three months previous to her admission to the Peter Bent Brigham Hospital an ulcer of the esophagogastric junction had been demonstrated by roentgenogram. The stools showed occult blood (2 plus by the guaiac test), and she had moderately severe anemia, as shown by a red blood cell count of 3,850,000 and a hemoglobin content of 7.87 Gm. Roentgen examination showed that the esophagus ended 10 cm. above the diaphragm, with an ulcer at the distal end. The fundus of the stomach was herniated through the esophageal hiatus.

CASE 2.—A 53 year old woman, married, stated that three months before admission she had experienced a severe attack of asthmatic bronchitis following a cold. Since then there had been a frequently recurring cough with wheezing. During this time she also had a "squeezing hurt" substernally, not related to exertion but frequently occurring after breakfast. Three years previous to entrance she had nausea and vomiting; her condition at that time was diagnosed by roentgenogram as duodenal ulcer, and her symptoms were relieved by diet. She had diverticula of both the sigmoid and the transverse colon. No anemia was present, and no occult blood was demonstrated in the feces. Roentgen examination on this admission to the hospital showed that the esophagus ended 4 cm. above the diaphragm. A portion of the fundus of the stomach wes herniated through the hiatus. No ulcer was seen.

CASE 3.—A 60 year old woman, single, complained for a number of years of an upper abdominal pain accompanied by gas; however, the pain was intermittent in character; at times during the past six months it had disappeared for several days. When she had pain, she ate no food, drank hot water and was generally relieved. Headaches and constipation had

6. Harrington, S. W.: Esophageal Hiatus Diaphragmatic Hernia, J. Thoracic Surg. **8**:127 (Dec.) 1938.

7. Moersch, H. J.: Hiatal Hernia, Ann. Otol., Rhin. & Laryng. **47**:754 (Sept.) 1938.

8. Jones, C. M.: Hiatus Esophageal Hernia, with Special Reference to Comparison of Its Symptoms with Those of Angina Pectoris, New England J. Med. **225**:963 (Dec. 18) 1941.

9. Bailey, P.: A Case of Thoracic Stomach, Anat. Rec. **17**:107 (Oct.) 1919.

10. LeWald, L. T.: Thoracic Stomach: Differentiation from Eventration and Hernia of the Diaphragm, Radiology **3**:91 (Aug.) 1924.

11. Truesdale, P. E.: Diaphragmatic Hernia at the Esophageal Hiatus, New England J. Med. **212**:240 (Feb. 7) 1935.

increased in frequency. She had moderately severe anemia, characterized by a hemoglobin content of 11.59 Gm. and a red blood cell count of 3,780,000. The feces were positive for occult blood (1 plus by the guaiac test). Roentgenograms of the upper part of the gastrointestinal tract showed that the esophagus ended 5 cm. above the diaphragm and that the fundus of the stomach herniated through the esophageal hiatus. Diverticulosis of the colon was demonstrated by a barium sulfate enema.

CASE 4.—A 56 year old man was first seen in the outdoor department in June 1927, complaining that he had suffered from pain in the left lower quadrant of the abdomen for the past four weeks. This pain came on while he was eating and radiated to the front of the chest, where it seemed to choke him and where it seemed to cause him to regurgitate food several times after eating. Five months later he was seen again, at which time he complained of midabdominal pain which came immediately after eating and radiated up to the throat. The pain was relieved by eructation of gas. Roentgen studies at that time revealed a duodenal ulcer and a hiatal hernia. Five years later he was seen again and said that he had never been free of the aforementioned symptoms for any length of time during the preceding five years and that of late they had become worse. At this time he also complained of pain on reclining at night. Roentgen examination again showed a duodenal ulcer and hiatal hernia. Four months later another roentgen examination was made, at which time a congenitally short esophagus and a duodenal ulcer were diagnosed. The esophagus ended 6 cm. above the diaphragm. Esophagoscopy failed to demonstrate a thoracic stomach.

CASE 5.—A 77 year old woman, married, had complained for the past six months of vomiting immediately after meals about every other day. For some time she had noticed also that food when swallowed seemed to stick at the lower part of the chest. For this reason she could eat only soft and semisolid foods. Roentgen examination showed a congenitally shortened esophagus ending 5 cm. above the diaphragm with a part of the fundus of the stomach above the diaphragm.

CASE 6.—A 51 year old housewife said that for many years she was unable to lie on her left side because of a sensation as of something running up and down inside her chest. Substernal fulness and pain occurred after a meal of coarse foods and about 5 o'clock each morning, relieved by rubbing. Occasional spells of dizziness followed by vomiting were experienced for several years. She always vomited easily, without nausea, and then felt relieved. One of three roentgen examinations showed a congenitally short esophagus. All showed dilatation of the esophagus without obstruction and herniation of the fundus of the stomach through the esophageal hiatus—freely movable.

CASE 7.—A 58 year old man gave a history of loss of weight and strength associated with discomfort in the lower part of the abdomen, relieved by reclining, not always associated with ingestion of food or relieved by it. Nausea and vomiting had occurred on four occasions during the past year after eating. Roentgen examination showed a congenitally short esophagus with delay at the third portion. The stomach was above the diaphragm, behind the heart, and fixed upside down. The distal transverse colon and the sigmoid were also herniated through the hiatus. The patient also had pernicious anemia with an initial hemoglobin level of 6.21 Gm. and 1,570,000 erythrocytes per cubic millimeter of blood. His anemia was successfully controlled for six years, at the end of which time death followed an attack of pneumonia.

Symptoms.—Six of the patients with a congenitally short esophagus were troubled with vomiting or regurgitation after ingestion of food. In only a single instance was nausea mentioned. The distress or pain was usually relieved by the regurgitation.

Substernal pain or distress or a feeling of obstruction in this location was present in 5 patients. This occurred either after ingestion of food, especially coarse food, or while the patient was reclining, and frequently was relieved by vomiting.

Abdominal distention, accompanied by gas, occurred in 2 cases, and discomfort in the lower part of the abdomen, relieved by reclining, occurred in 1. Cough, accompanied by asthmatic wheezing, was a prominent complaint of 1 patient, but the evidence is not sufficient to indicate that it was related to the herniation

Goodall and Hoyt [12] reported dyspnea as the most prominent symptom of 3 patients, 2 of whom probably had complete thoracic stomach. They expressed

12. Goodall, H. W., and Hoyt, L. H.: Thoracic Stomach, Arch. Int. Med. **53**:594 (April) 1934.

the belief that the stomach lying within the thorax interfered with respiration, causing dyspnea.

It is of interest to note that in our series of patients symptoms which suggest disturbance of the gastrointestinal tract predominated and that they were so distinctive that the diagnosis should have been strongly suspected before roentgen studies were made.

Severe anemia was demonstrated in 2 patients. One of them (case 7) had pernicious anemia; the other had rather profuse hemorrhage, which probably resulted from an ulcer at the esophagogastric junction. A third patient had moderately severe anemia. One patient's blood was not examined. In 2 instances a duodenal ulcer was diagnosed, but in neither was there anemia or symptoms strongly suggestive of ulcer.

HIATAL HERNIA

Mention has already been made of some factors which may influence the development of herniation. Marks [5] and also Levy and Duggan [1d] suggested that obesity is an important contributory factor. Marks expressed the belief that increased intra-abdominal pressure, which may be produced by more than the normal amount of fat in the omentum, a large fibroid or a pregnant uterus, may produce herniation. Rigler,[1c] as mentioned previously, emphasized the importance of pregnancy as a factor. Thirty-seven patients, or slightly more than one half of our series of 72, were women who had been pregnant one or more times.

Trauma is undoubtedly responsible for herniation in some cases. One patient, previously mentioned, had symptoms which were later considered to be the result of a hiatal hernia developing after a fall from a stone wall. Two other patients referred the onset of symptoms to accidents in which their heads were forcibly bumped against the top of an automobile as it went over a bump in the road at a high rate of speed. It seems likely that any one of the factors mentioned might produce herniation in a person with a congenitally defective or relaxed esophageal hiatus whereas none of the same factors might be sufficient to produce herniation in a patient with a normally formed hiatus.

Symptoms.—The histories of the 7 patients with congenitally short esophagus are included in the following analysis of symptoms because there seemed to be little difference between the two groups. For the same reason the histories of 7 patients who also had pernicious anemia are included.

Pain was the symptom most frequently stressed by the patients. Since the description of the sensations varied greatly from one person to another, it is difficult to know just which expressions of discomfort should be included in this category. The term "pain" is used here to include such recorded sensations as dull or sharp pain, distress, ache, squeezing sensation and feeling of fulness or of obstruction on the swallowing of food.

Fifty-nine of the 72 patients had pain which was believed to be related to hiatal hernia. The pain was said to be in the substernal region by 23 and in the upper part of the epigastrium by 33; 56 patients had some sort of discomfort over an area extending from the middle of the chest to the upper part of the epigastrium. Other sites for the location of pain were: the right upper quadrant of the abdomen eight times; right side of the chest three times; the precordial region three times; the left side of the chest, the lower part of the abdomen, the back rarely. If one takes into consideration the facts that the histories were recorded by several physicians and that in many instances hiatal hernia was not suspected, it appears significant that the discomfort was so frequently localized within a rather limited area.

The pain was described as dull (ache or squeeze) by 32 patients and as acute or sharp by 12. It radiated to the abdomen in 9 instances, to the back in 4, to the left arm and shoulder (suggesting anginal pain) in 4, to the right shoulder and arm in 3 and to both the right and the left shoulder in 3.

Discomfort was initiated or aggravated by a meal in 21 instances, by solid food in 9 and by water in 2, making a total of 32 instances in which pain was experienced after ingestion of food or water. Reclining initiated discomfort in 16 cases, whereas exercise, especially that involving the moving or lifting of heavy objects, accounted for the onset in 7. Emotional upsets not infrequently aggravated the condition. Both reclining and lifting are probably much more frequent causes of discomfort than is suggested by these figures. The patient is frequently not aware of the precipitating or aggravating factors, and unless the physician recording the history includes hiatal hernia in his differential diagnosis, these factors may not be brought out in the anamnesis.

Relief from symptoms was attributed to ingestion of an alkaline drink in 7 instances; to that of soft food in 6; to taking of whisky in 1; to vomiting in 14; to use of glyceryl trinitrate in 3; to application of heat in 3; to rest in bed in 2, and to eructation of gas in 1.

Anemia rates second to pain in order of frequency of occurrence as a symptom in our series, and this subject will be discussed later in some detail.

Other symptoms, grouped as they were mentioned in the records, occurred as follows: vomiting, in 32 instances; nausea, in 19; gas in the stomach, in 19; weakness or easy fatigability, in 13; diarrhea, in 10; heartburn, in 9; constipation, in 9; anorexia, in 8; headache, in 7; indigestion, in 4; cough, in 4; nervousness, in 3; insomnia, in 2; dizziness, in 2.

The history most characteristic of patients with hiatal hernia may be summarized somewhat as follows: Following ingestion of food, particularly solid or coarse, there is a feeling of obstruction or pain (ache or squeeze) in the substernal or the upper epigastric region. This may be followed by regurgitation or vomiting, with relief of symptoms.

Discomfort in the same regions as those described in the foregoing paragraph may occur on reclining, especially during the night, and be relieved on arising; or there may be distress after lifting or moving heavy objects. Either reclining or lifting may be followed by hemorrhage, which is in some instances the cause of anemia, as discussed later.

Vomiting and regurgitation of food not associated with nausea are very characteristic complaints. Unexplained indigestion associated with "gas," heart burn or anorexia and easily produced weakness must each lead one to think of hiatal hernia.

Healy [13] summarized the symptoms of his patients as follows: "The most common symptom we found in our cases was substernal pain with regurgitation when in the supine position. The next in order is the vague gastric distress sometimes with tenderness referable to the right upper quadrant and not in the epigastric region, accompanied at times by pain radiating to the back similar to a gall stone attack. Then came vomiting in the morning with hyperacidity. Only in a very few cases did we note difficulty in swallowing solid food at times."

Pancoast and Boles [14] stated that symptoms may be entirely absent but that "probably the most constant, certainly the most suggestive, symptom present is

13. Healy, T. B.: Symptoms Observed in Fifty-Three Cases of Non-Traumatic Diaphragmatic Hernia, Am. J. Roentgenol. **13**:266 (March) 1925.

14. Pancoast, H. K., and Boles, R. S.: Non-Traumatic Left Diaphragmatic Hernia, Arch. Int. Med. **38**:633 (Nov.) 1926.

pain, often of a colicky nature, localized just above the ensiform or in the epigastrium, which comes on gradually and more often when the patient is lying down, especially at night."

Ohnell [15] found pain in the epigastrium or the immediate neighborhood in 16 and burning or pressure in the same location in 3 of 24 cases reported in the literature. Pain usually occurred immediately or within two to three hours after ingestion of food. Vomiting occurred in 10, regurgitation or heartburn in 6, dysphagia in 4, constipation in 5 and cardiac or pulmonary symptoms in 4 instances.

Goodall and Hoyt [12] have presented in considerable detail the symptom complex observed in their 5 cases, stressing particularly the preponderance of symptoms referable to interference with cardiorespiratory function in 3 patients with thoracic stomach.

Harrington [3] stated that "the chief symptoms of esophageal hiatus hernia are pain, distress, gaseous eructation, vomiting, dyspnea, hemorrhage, weakness, anemia, and palpitation of the heart." He divided the symptoms into those occurring early and those occurring late in the course of the herniation, the main difference being in the severity and the frequency of occurrence. The epigastric distress may be projected through to the back during or shortly after a heavy meal or even after a cup of coffee, and is often relieved by belching of gas and vomiting; this pain is often attributed to cholecystitis.

Jones [8] compared the symptoms of 91 patients with small and 37 with large hiatal hernias. Substernal pain was experienced by more than one third of those with small but by only 5 of those with large hernias. Otherwise there was little difference in the two groups which could be definitely ascribed to the size of the herniation. It is of interest to note that on the basis of the clinical picture a diagnosis of heart disease was made in 13 and of disease of the biliary tract in 22 cases of his series.

These reports and others less concretely summarized, although not in entire agreement in respect to the most characteristic complaints, confirm our own observation that the symptoms are predominantly gastrointestinal in nature and that in a high percentage of instances they are characteristic of the condition so that the diagnosis should be suspected and roentgen examination should merely confirm the diagnosis.

That hiatal hernia occurs more commonly than it is recognized has been noted particularly by Healy,[13] who emphasized the importance of diagnosing the condition correctly so that operations performed because of a confusion of symptomatology would be avoided. Pancoast and Boles,[14] Weitzen,[16] and others have also commented on the importance of avoiding operation on the gallbladder or for peptic ulcer because of failure to recognize the true cause of the symptoms, that is, hiatal hernia.

Roentgenologic recognition of a hiatal hernia even when the presence of the hernia is suspected from the clinical picture is not always possible. At least 14 of our series of patients had been examined by roentgenogram one or more times before the herniation was demonstrated. Two others showed no evidence of herniation after medical treatment had been carried out for several months following demonstration of the hernia. Levy and Duggan [1d] reported 4 of 26 cases in which previous roentgen studies had failed to show herniation.

15. Ohnell, H.: Hernia diaphragmatica hiatus oesophagei vom intern klinischen Gesichtspunkt, Acta radiol. **6**:23, 1926.

16. Weitzen, M.: Diaphragmatic Hernia with Severe Anemia, Am. J. Roentgenol. **28**:808 (Dec.) 1932.

Failure to realize the importance of herniation as the cause of the most disturbing symptoms present in conjunction with those from other pathologic conditions is a common error. Gastroenterostomy was performed in 1 patient because of the presence of a duodenal ulcer, but a few years later the original complaints returned and a hernia was demonstrated. A cholecystectomy not followed by relief of symptoms was recorded in a few instances. Angina pectoris or coronary infarction was believed to be present in several instances, but in only 1 case did an electrocardiographic tracing show evidence of coronary disease; the patient later died of an infarction. A diagnosis of psychasthenia was recorded in a surprisingly large number of instances, apparently because of complaints, often extending over many years, for which no satisfactory explanation in the form of organic disease was demonstrated, although hiatal hernia was known to be present in a few instances.

Earlier in the paper it was mentioned that anemia as a symptom of hiatal hernia was next to pain (or discomfort of a sort sufficiently intense to be classed as pain) in frequency of occurrence. An analysis of the blood was made in 67 of the 72 cases of this series. A diagnosis of pernicious anemia was made in 7 instances and treatment by the usual methods completely controlled the blood levels. In 2 other cases there was severe macrocytic anemia with a high color index, which may best be diagnosed as idiopathic macrocytic anemia.

Forty-seven, or 70 per cent, of the 67 patients tested had hemoglobin levels of 12 Gm. or less and 4,000,000 or less erythrocytes per cubic millimeter. If one excludes the 7 patients with pernicious anemia, there were 40, or 66 per cent, with anemia of some degree. Twenty-three patients, or 34.3 per cent, had hemoglobin levels lower than 10 Gm. and erythrocyte counts less than 3,300,000. If the 7 patients with pernicious anemia are excluded, there were 16, or 26.6 per cent, with a severe anemia at some time during their observation, possibly caused by the hiatal hernia. In several cases the determination of the blood levels was not done soon enough after a known hemorrhage to demonstrate the maximal degree of anemia.

The cause for the presence of anemia was in some instances open to question, since a gross, severe hemorrhage was not demonstrated in all instances of severe anemia. In a few cases a peptic ulcer or a carcinoma may have been the cause of the hemorrhage observed. Eighteen patients were known to have gross and rather profuse loss of blood. Two others became suddenly dizzy and fell because of weakness, but since neither one consulted a physician for several days, hemorrhage was not demonstrated. A guaiac test of the feces was made in 51 cases; in 18 the result was negative, in 12 it was 1 plus, and in 21 it was 2 plus or stronger.

Peptic ulcer was diagnosed roentgenologically at some time in 9 patients. One with an esophageal ulcer had moderately severe hemorrhage and severe anemia. Two with gastric ulcers had no demonstrable massive hemorrhage, but both had a positive guaiac test of the feces and slight anemia. One of 6 patients with duodenal ulcers had several massive hemorrhages and became severely anemic after each. The diagnosis of duodenal ulcer was made, but the hernia was not demonstrated before he was seen by one of us (W. P. M.). Roentgen studies at the Peter Bent Brigham Hospital demonstrated the herniation, but no ulcer could be visualized. Two of his attacks of hemorrhage occurred in the early morning, after a night in bed, during periods when he was unusually tired, and a third followed the lifting of some heavy boxes and furniture. The patient was advised to have his hernia surgically repaired in order to prevent further hemorrhages. Instead gastroenterostomy was performed in another hospital after a fourth hemorrhage, after which he died from embolism. A positive guaiac test of the feces

was recorded for 3 others of the 6 patients with duodenal ulcers, none of whom was anemic.

One of the 2 patients with carcinoma of the stomach had severe hemorrhage and was severely anemic. The other one was not anemic.

It is obvious that the demonstrated peptic lesions could not be responsible for the anemia in a high percentage of instances and that both massive hemorrhage and anemia in this series of patients can probably most commonly be explained on the basis of the hiatal hernia. It is likewise evident that the anemia observed was the result of massive hemorrhage only in a small percentage of instances. It seems likely that the anemia is often the result of prolonged loss of small amounts of blood from the congested esophageal or gastric mucous membrane constricted within the esophageal hiatus. Definite evidence of nutritional deficiency because of an inadequate intake or utilization of food was lacking.

It is difficult to determine the frequency of occurrence of anemia in hiatal hernia in the published series because this aspect has been considered in but few. Harrington [3] reported anemia in 11 per cent of 198 patients on whom he had operated for hernia. The degree of anemia, however, was not mentioned. He emphasized the importance of "secondary" anemia as a clinical manifestation of hiatal hernia. Cowan [17] reported the presence of "secondary" anemia in 13 of 45 cases reviewed but recorded the blood levels in only 2. Marks [5] found erythrocyte levels below 4,000,000 in 7 of 29 patients but stated that not much attention was paid to the anemia. Two of his patients had massive hemorrhage at some time. Levy and Duggan [16] reported anemia in only 1 of 26 patients observed. Weitzen [16] reported 2 patients with the association of anemia and hiatal hernia. Segal [18] reported 2 patients of his own and 3 from the literature in whom the only symptom resulting from hiatal hernia was anemia. He recorded 5 other cases from the literature in which anemia was present. Gardner [19] reported 6 of his own patients and 22 found in the literature in whom severe anemia and hiatal hernia were associated. No other possible cause for the anemia was demonstrated in 20 of these, although the figures recorded indicate that a high color index was present in 1. Blood levels are recorded for only 2 of 10 patients reported by Andrews.[20] One of these was severely, the other moderately, anemic. Neither ulcers nor hemorrhages were observed in her series. Others have also reported isolated instances of anemia. Since these are not related to any series of cases, the incidence cannot be determined.

There is some difference of opinion as to the cause of the anemia observed in patients with hiatal hernia. Harrington [6] spoke of hemorrhage as a not uncommon occurrence. He expressed the belief that it is the result of an ulceration, usually at the lower end of the esophagus, produced by trauma of the incarcerated stomach. He also expressed the belief that these ulcerations are rarely demonstrated by roentgen examination but more commonly by esophagoscopy. Bock, Dulin and Brooke,[21] who reported the presence of "secondary" anemia in 10 patients with hiatal hernia made the comment: "Bleeding may be from coexisting ulcer but is usually from mucous congestion."

17. Cowan, I. I.: Diaphragmatic Hiatus Hernia, Am. J. Roentgenol. **37**:333 (March) 1937.
18. Segal, H. L.: Secondary Anemia Associated with Diaphragmatic Hernia, New York State J. Med. **31**:692 (June 1) 1931.
19. Gardner, K. D.: Diaphragmatic Hernia Associated with Secondary Anemia, Am. J. M. Sc. **185**:561 (April) 1933.
20. Andrews, K. S.: Diaphragmatic Hernia, with Report of Ten Cases of Oesophageal Orifice Hernia, Am. J. Digest. Dis. & Nutrition **2**:310 (July) 1935.
21. Bock, A. V.; Dulin, J. W., and Brooke, P. A.: Diaphragmatic Hernia and Secondary Anemia: Ten Cases, New England J. Med. **209**:615 (Sept. 28) 1933.

The fact that anemia has not been previously associated commonly with hiatal hernia may lead to the impression that our series may be somewhat unusual in that many of the patients might have come to our attention primarily because of an unusual interest in anemia. However, only 15 of the 72 patients are included from the private records of one of us (W. P. M.). The incidence of anemia in this series of patients should lead to a more serious consideration of it as a symptom of hiatal hernia. Hypochromic anemia for which no cause is readily demonstrated, particularly if associated with the symptom complex described, should lead one to suspect seriously the presence of a hiatal hernia.

Gastric analysis was performed in only 34 cases, in 12 of which achlorhydria was shown whereas in 22 essentially normal amounts of acid were found. Seven of the 12 patients with achlorhydria had pernicious anemia. One patient showed achlorhydria at a time when the herniation was demonstrable by roentgenogram, but after a few months of therapy the hernia was not demonstrable, and free hydrochloric acid was found to be present. It seems likely that at the time of the first test the tube did not actually reach the secreting portion of the stomach. This possibility must be kept in mind if the gastric test shows achlorhydria.

Disease of the gallbladder was diagnosed by roentgen examination in 13 patients of the series, and a diagnosis of carcinoma of the gallbladder was made in 1 of these. Diverticulosis of some portion of the digestive tract was demonstrated in 16. There is no reason to believe that any of these conditions was the cause of the anemia.

Treatment.—Surgical intervention may be necessary in some instances and is desirable particularly if the symptoms indicate that the the hernia is becoming more severe. It is a treatment of necessity when there is incarceration of the stomach in the esophageal hiatus with symptoms of obstruction and with recurrence of severe hemorrhage. Ohnell [15] found that 10 of 24 patients whose cases were reviewed as recorded in the literature died from strangulation of the hernia and that 2 died from inanition. He advised medical treatment only for those whose condition was unsuited to surgical treatment. Key [22] and also Pancoast and Boles [14] expressed the opinion that surgical operation is the only effective treatment except in the case of congenitally short esophagus. Harrington [3] likewise supported the concept that surgical operation is the treatment of choice whenever it may be expected to be successful. He has reported 198 cases in which he operated.

The reports found in the literature present little information concerning either the death rate following operations or the extent of successful results in controlling symptoms from which one may draw conclusions in regard to the comparative value of surgical and medical management. Jones [8] expressed the belief that treatment should be essentially medical and that phrenicectomy or surgical repair is justified only for the large hernia or when medical measures fail.

As a result of the evidence presented in our series of cases and particularly as a result of actual use of medical management for those under the private care of one of us (W. P. M.) it may be concluded that the great majority of patients, particularly during the earlier stages of herniation, may be controlled satisfactorily by medical treatment provided the complete cooperation of the patient is obtained. The more severe manifestations, therefore, should be avoided.

Medical management should include the following:

At first the patient should be given a diet low in roughage, with avoidance of solid foods; later the diet should be increased to include some moderately rough and

22. Key, E.: Hernia diaphragmatica hiatus oesophagei vom chirurgisch-therapeutischen Gesichtspunkt, Acta radiol. **6**:35, 1926.

coarse foods. Such a diet may include puréed vegetables. It should be divided into five or six small meals daily rather than the customary three larger ones. At no time should the stomach be overloaded. Loss of weight will be desirable in the obese patient.

Patients should be advised to rest before meals. Although some may be able to recline, many will feel better resting in a sitting position or partially reclining. In no case should the patient recline soon after a meal. Those patients whose symptoms occur at night or on reclining will be benefited by sleeping in a semi-reclining position. This may be accomplished by banking pillows, raising the head portion of the mattress, or raising the head of the bed on blocks 3 or 4 inches (7.5 or 10 cm.) high.

The patient should be cautioned against lifting heavy objects or lifting any object from a bending over position. All straining and other pronounced physical effort should be avoided, particularly if the patient is obese.

The hypochromic anemia resulting from loss of blood should be treated in the usual manner with optimal doses of iron.

CONCLUSIONS

Hernia at the esophageal hiatus is sufficiently clearcut and distinct symptomatically from the commonly recognized pathologic conditions of the upper part of the abdomen and of the thorax that it should be more frequently included in the differential diagnosis of disease in these regions.

Anemia is so commonly associated with hiatal hernia that its presence may be logically explained on the basis of the hernia, and it must be considered an important aid in the diagnosis. It is usually hypochromic and the result of hemorrhage arising from ulceration of the esophageal or of the gastric mucosa or from congestion of the mucous surfaces, produced in either case by mechanical interference by the esophageal hiatus.

The important role of hiatal hernia in the production of certain distressing or incapacitating symptoms and of anemia should be recognized, so that proper medical treatment may be instituted for their relief, which may also prevent the occurrence of the more serious manifestations of the condition.

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ASSOCIATION OF CIRRHOSIS, THROMBOPENIA AND HEMORRHAGIC TENDENCY

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The hemorrhagic phenomena, so often a complication of hepatic disease, has long presented a serious medical problem, particularly when the disease is severe and of long duration. The isolation of vitamin K and its application to control of the hemorrhagic tendency in hepatic disease created the impetus for study which has increased appreciation of the role of the liver in the synthesis of factors necessary for normal coagulation of blood. For many years thrombin has been known to play a definite part in coagulation of blood, and its precursor, prothrombin, has been shown to be a product of hepatic metabolism. It now is known that a normally functioning liver is one factor necessary for the maintenance of a normal level of prothrombin in the plasma.[1]

Experimentally and clinically, it has been demonstrated that in certain diseases of the liver, a diminished level of prothrombin in the blood often is restored to normal if an adequate amount of vitamin K is made available. However, in severe parenchymal damage to the liver, it is not uncommon to find that despite availability of adequate vitamin K, an adequate concentration of prothrombin cannot be maintained in the blood plasma. This lack of response to the administration of vitamin K can be used as a clinical measure of the degree of hepatic damage present. The quantitative response of prothrombin formation to the administration of vitamin K parallels the clinical state of the liver, and it has been suggested that this response be used as a test to aid in differentiating jaundice due to primary intrahepatic disease from that secondary to obstruction of the biliary passages.

Because of the known effect of the administration of vitamin K on the maintenance of a normal level of prothrombin in the blood in hepatic disease, the administration of this vitamin often is thought to be all that is necessary in cases of such disease to insure a normal clotting time of the blood, and it is forgotten that other factors essential to the complicated physiologic process of blood clotting may be deficient or absent and by their lack prevent normal clot formation. This truth recently was brought rather forcibly to our attention in case 1.

CASE 1.—A woman 46 years of age for approximately twenty years had experienced recurrent attacks of epigastric pain without jaundice. Three years prior to her arrival at the Mayo Clinic she had undergone cholecystectomy for calculous cholecystitis; the common duct was not explored. Jaundice followed this operation, and, to correct this, one month later, in May 1938, the common duct was explored and a T tube was inserted. The jaundice cleared and did not return as long as drainage was adequate through the T tube. In April 1939 an unsuccessful attempt was made to anastomose a hepatic duct to the gastrointestinal tract. Jaundice recurred

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Read at the First Annual Meeting of the American Federation for Clinical Research, Minneapolis, April 20, 1942.

1. Andrus, W. D., and Lord, J. W., Jr.: Clinical Investigations of Some Factors Causing Prothrombin Deficiency: Significance of the Liver in Their Production and Correction, Arch. Surg. **41**:596-606 (Sept.) 1940.

and never entirely cleared after this procedure. A final unsuccessful attempt to establish a connection between the biliary system and the gastrointestinal tract was made in April 1940.

The patient registered at the clinic in October 1941 because of persistent jaundice, attacks of chills, fever, pruritus and colicky pain in the right upper quadrant of the abdomen, which would extend into the right subscapular region if severe. She did not give a history of a tendency to bleed.

On examination the patient was seen to be markedly jaundiced; the skin had the characteristic bronzing of long-standing icterus. The right side of the diaphragm was elevated to the level of the sixth rib posteriorly and was immobile. The liver and spleen were enlarged and firm; their borders extended approximately 6 cm. below the costal edge. The blood pressure was normal. The flocculation test for syphilis gave negative results; albuminuria, grade 2, was present. Roentgenograms of the stomach and colon revealed nothing abnormal. That the liver was damaged considerably was evidenced by a total excretion of hippuric acid of 1.4 Gm., as compared with a normal excretion of approximately 3 Gm. Macrocytic hypochromic anemia with 9.75 Gm. of hemoglobin per hundred cubic centimeters of whole blood was present. The serum bilirubin amounted to 15.2 mg. per hundred cubic centimeters. The qualitative van den Bergh reaction was direct. Several preoperative estimations of the prothrombin time by the Quick method gave results varying between seventeen and twenty-three seconds, as compared with a normal value of nineteen seconds.

It was felt that further surgical exploration of the biliary system was advisable, and to this end the patient was prepared in the usual manner by means of a diet high in carbohydrate, low in fat and moderate in protein content. Ten per cent solution of dextrose to which was added thiamine chloride, nicotinic acid amide and ascorbic acid was administered intravenously. A daily dose of 3.2 mg. of 2-methyl-1, 4-naphthohydroquinone-3-sodium sulfonate was administered intravenously for two weeks as a source of vitamin K. The Quick prothrombin time was normal on the day of operation. Incision was made through the old abdominal scar, which was found to be thick and dense. At the outset bleeding was encountered so profuse that all the usual measures to control it were unsuccessful. It therefore was necessary to discontinue the operation. The surgeon remarked that the bleeding was so continuously severe that it demonstrated a lack of all tendency to clot. The hemorrhage was controlled finally by pressure; the wound was closed and a transfusion of 500 cc. of whole blood was given. The patient made a satisfactory convalescence, and no further tendency to bleed was evident during the remainder of her stay in the hospital.

Our interest was roused by the unusual complication, and further studies were made of the bleeding and coagulating factors of the blood during convalescence. Two platelet counts by the citrate method were, respectively, 68,000 and 56,000 per cubic millimeter of blood. The bleeding time was recorded as six minutes and three and a half minutes on two estimations; the coagulation time was eight minutes; the clot retraction was partial in twenty minutes and complete in fifty minutes. These values are essentially normal with the exception of the obvious reduction in the number of thrombocytes present.

Here, then, was a case in which there was no suggestion before operation of an unusual tendency to bleed. Moreover, the Quick prothrombin time was normal, and this we have learned to recognize as a safe index of the clotting power of the blood of jaundiced patients. If before operation we had been unduly apprehensive about the hemorrhagic tendency and performed more detailed studies of coagulation time, bleeding time and the number of thrombocytes, our suspicions probably would not have been aroused, because these values, of which all but the last were normal during the convalescent period, probably would have been the same immediately before operation. Fortunately, such a serious hemorrhagic tendency is not often encountered in cases of jaundice when the prothrombin time is normal and an adequate supply of vitamin K has been administered. Since the thrombocytes were the only constituent of blood known to be grossly abnormal, it appeared to us that depletion of them was a significant factor in the hemorrhagic tendency in this case. This observation seemed to deserve further consideration in order that the frequency with which significant thrombopenia is present in cases of severe disease of the liver and its relation to the tendency to bleed in these cases might be determined.

Snell, Vanzant and Judd [2] in 1930 called attention to the occurrence of severe thrombopenia in a case of long-standing hepatic disease and noted that the depression of the thrombocytes in the blood was parallel to the hemorrhagic tendency. We are reviewing briefly this case, which elsewhere is recorded in detail,[2] because it represents one of the first observations of a significant reduction in the blood platelets in a case of severe hepatic damage:

CASE 2.—A woman 29 years of age had had cholecystectomy for calculous cholecystitis one year prior to her admission to the Mayo Clinic. Bile began to drain from the wound on the third postoperative day, and jaundice appeared after permanent closure of the biliary fistula ten months later. Deepening of the jaundice was accompanied by mild purpuric manifestations and a tendency to increased menstrual bleeding.

On examination, in addition to the jaundice and purpuric manifestations, mild secondary anemia was noted. After preparation choledochostomy was performed for benign stricture of the common duct, and a T tube was left in place. After operation the tendency to hemorrhage was great and was controlled only by repeated transfusions of blood. The patient made a good recovery and was allowed to return home. When she was seen three months later, her serum bilirubin was found to be 2.7 mg. per hundred cubic centimeters, and the coagulation time was slightly elevated (twelve and one-half minutes). The fistula had continued to drain copious amounts of bile, and her general health was much improved.

The fistula closed spontaneously five months after the operation, and the patient immediately returned to the clinic. At this examination the jaundice had already definitely increased; the serum bilirubin was 4.7 mg. per hundred cubic centimeters. A few days after admission bleeding began from the gums, nose, skin and uterus, and signs of meningeal irritation appeared, which were interpreted as being due to meningeal hemorrhage. The patient became semicomatose and manifested irritability, photophobia and diplopia, and Kernig's sign was present. Repeated transfusions of blood caused temporary improvement. Drainage of bile was reestablished, but there was no improvement in the coagulation factors of the blood. The number of blood platelets per cubic millimeter of blood, which had been 198,000 when the patient was first examined, now ranged between 40,000 and 94,000. The bleeding time determined by the usual technic was normal, but wounds in the skin frequently reopened and bled many days after the puncture was made. The prothrombin time greatly increased. The tourniquet test gave slightly positive results, and the coagulation time varied from twenty to forty minutes. The clot, once it was formed, was normal. Five weeks after the first signs of meningeal irritation the patient suddenly became somnolent. Puncture wounds a week old dribbled blood in a steady stream, and the entire body was covered with great regions of ecchymosis. The venous blood became virtually incoagulable, and death finally resulted.

At necropsy, in addition to the jaundice and external evidence of bleeding noted during life, extensive hemorrhages were found throughout the gastrointestinal tract, the peritoneal cavity, the substance of the lungs and the mucous membrane of the urinary bladder, and there was evidence of severe hemorrhages, both old and new, in the dura mater, the arachnoid and the substance of the brain. The histologic picture of the liver was that of biliary cirrhosis.

The authors in their comment drew particular attention to the depression of the thrombocytes in this case, although they did not claim that this factor was the most significant one in the hemorrhagic tendency. In the light of present knowledge of the value of vitamin K in such cases it is apparent that the administration of this vitamin probably could have changed the clinical course. The prothrombin time was markedly increased, and it is probable that inadequate synthesis of prothrombin by the liver was responsible for the depletion of the prothrombin level in the blood. This inadequate synthesis of prothrombin can be attributed in part to the severe hepatic damage and in part to the inability to utilize what vitamin K was present, because of the complete exclusion of bile from the intestinal tract for such an extended period. It is significant, however, that a profound depletion in blood platelets also was present, and this additional factor undoubtedly contributed in part to the severe hemorrhagic tendency.

These 2 cases represent a distinct type of serious hepatic disease, and in both of them significant thrombopenia was associated. In case 1 the lesion was essentially

2. Snell, A. M.; Vanzant, F. R., and Judd, E. S.: The Complications and Sequelae of Prolonged Obstructive Jaundice, M. Clin. North America **13**:1417-1438 (May) 1930.

biliary cirrhosis secondary to severe obstructive jaundice of long standing; in case 2, there was in addition to severe biliary cirrhosis the factor of prolonged extensive loss of bile from the external fistula. That an equally significant depletion in the thrombocytes in the blood with a tendency to bleed is associated with severe hepatic damage of a different type is demonstrated in case 3.

CASE 3.—A farmer aged 53, with a good family and personal history, experienced recurrent epigastric distress for fifteen years. He was a moderate user of alcohol and tobacco. Five months before he came to the clinic he noted an exacerbation of his epigastric distress and progressive abdominal enlargement. Coincident with the enlargement of his abdomen purpuric manifestations became evident in the lower extremities, and these were more marked when he spent a great deal of time on his feet. On examination, he was obese, the abdomen was protuberant and dull to percussion and a fluid wave was demonstrable. The liver and spleen were palpably enlarged. Scattered petechiae were observed on the lower extremities; there was cervical and axillary lymphadenopathy. The blood pressure was 100 mm. of mercury systolic and 64 mm. diastolic. The Kline flocculation test of the blood serum gave negative results. The urine was normal. The concentration of hemoglobin was 13.5 Gm. per hundred cubic centimeters of whole blood. The number of leukocytes and the differential count were within normal limits; there was macrocytosis. The concentration of serum bilirubin was 1.4 mg. per hundred cubic centimeters, with an indirect van den Bergh reaction. The bromsulphalein test of hepatic function showed retention of dye, grade 1. The bleeding time was one and a half minutes, and the Lee-White coagulation time was nine and a half minutes. The Quick prothrombin time was twenty-two seconds, as compared with a normal of twenty seconds. The number of blood platelets per cubic millimeter of blood estimated on four successive days was, respectively, as follows: 78,000, 124,000, 100,000 and 87,000. The values for blood urea, plasma cholesterol and cholesterol esters were, respectively, 28, 225 and 155 mg. per hundred cubic centimeters. The serum protein was 7 Gm. per hundred cubic centimeters, with an albumin-globulin ratio of 1:1.4. Peritoneoscopy and abdominal paracentesis were performed as a combined procedure. A considerable quantity of straw-colored ascitic fluid was removed, and the liver was seen to be involved by an extensive hobnailed cirrhosis grade 4. The patient was treated by the usual medical measures for cirrhosis, but he failed progressively and died six months later.

CIRRHOSIS OF THE LIVER

These observations induced us to review the records in a series of cases of cirrhosis of various types to see how often we would find a significant reduction in the blood thrombocytes in association with severe chronic hepatic disease. The majority of the cases studied were cases of portal cirrhosis, although some were included in which severe damage to the liver, so-called biliary cirrhosis, was secondary to an obstruction of the common duct of long standing. In the last-mentioned cases various degrees of clinical jaundice were associated with various elevations of the serum bilirubin. In each case of portal cirrhosis, injury of the liver was indicated by significant retention of the bromsulphalein dye at the end of one hour, and subclinical jaundice usually was associated with only slight elevation above normal of the serum bilirubin.

For this study we reviewed 80 cases of cirrhosis in which the blood platelet count had been recorded. The counts were made by the citrate method. With this method we have considered the normal concentration of platelets in the blood as from 150,000 to 300,000 per cubic millimeter. Counts varying from 100,000 to 150,000 were designated as borderline and those less than 100,000 as constituting a state of thrombopenia. Since it is known that serious bleeding may occur either spontaneously or as a result of minor trauma when the platelet count falls to less than 50,000, the counts varying from 50,000 to 100,000 were designated as subnormal and those less than 50,000 as critical. In 33 (41.3 per cent) of these 80 cases (table 1) bleeding of any kind did not occur. In 2 (6.1 per cent) of these 33 cases there was definite thrombopenia. In 28 cases (84.8 per cent) of those in which there was no bleeding tendency the platelet count was considered normal. The platelet count did not fall below the critical level in any case in this group. In

47 (58.7 per cent) of the 80 cases of cirrhosis a tendency to bleed was found (table 1). In 12 of these cases (25.5 per cent) a definite thrombopenia was present. In 2 cases the count was below the critical level, being 39,000 and 40,500 respectively. In only 20 cases of this group (42.6 per cent) was the platelet value normal. Bleeding was most commonly from the gastrointestinal tract but also was recorded as coming from the gums, nose, lungs and urinary bladder and occurred into the conjunctival sac and into the skin as purpuric spots and ecchymosis.

It is immediately apparent that the percentage incidence of a normal platelet value in cases of cirrhosis without bleeding was twice that in cases in which some degree of bleeding occurred. In 20 (41.6 per cent) of 48 cases in which the platelet count was normal, some bleeding tendency was present. In a total of 18

TABLE 1.—*Platelet Count in Cases of Cirrhosis of the Liver With and Without Bleeding*

Blood Platelet Count, per Cu. Mm.	Total Cases		With Bleeding		Without Bleeding	
	Number	Per Cent	Cases	Per Cent	Cases	Per Cent
Less than 50,000	2	2.5	2	4.3		
50,000 to 100,000	12	15.0	10	21.2	2	6.1
100,000 to 150,000	18	22.5	15	31.9	3	9.1
150,000 and over	48	60.0	20	42.6	28	84.8
Total	80	100.0	47	100.0	33	100.0
Mean count	197,000		165,000		242,000	

TABLE 2.—*Cirrhosis: Relation of Platelet Count to Bleeding Time and Lee-White Coagulation Time*

Blood Platelet Count, per Cu. Mm.	Bleeding Time			Lee-White Coagulation Time		
		Time Elevated *			Time Elevated †	
	Cases	Cases	Per Cent	Cases	Cases	Per Cent
Less than 100,000	9	3	33.3	5	1	20.0
100,000 to 150,000	9	3	33.3	9	1	11.1
150,000 or more	30	8	26.7	26	5	19.2
Total	48	14	29.2	40	7	17.5
Hemorrhagic manifestations	28	9	32.1	23	4	17.4
No hemorrhagic manifestations	20	5	25.0	17	3	17.6

* Any value of more than three minutes was considered elevated.
† Any value of more than ten minutes was considered elevated.

cases the count was borderline, and in 15 (83.3 per cent) of these bleeding tended to occur. In 10 (83.3 per cent) of the 12 cases in which the count was subnormal there was a tendency to bleeding. In both cases in which a critical count was found bleeding occurred. It is evident that of the cases of cirrhosis studied the tendency for some hemorrhagic manifestation to occur was twice as great in those in which the platelet count was subnormal or borderline as in those cases in which it was in the normal range.

The prothrombin time was estimated in 6 cases; in 3 of these bleeding had not occurred and in 3 bleeding of some type was noted. The prothrombin time was elevated in all but 2 cases, 1 from each group. Since the estimation had been made so infrequently, the incidence cannot be considered significant. In 48 cases the bleeding time was estimated (table 2). It was increased in about 32.1 per cent of the cases in which a hemorrhagic tendency was manifested and in only a slightly less percentage of cases (25 per cent) in which hemorrhage did not occur. This

estimation was too infrequently made to permit any conclusion to be drawn as to the significance of the apparently greater incidence of an elevated bleeding time in the cases of thrombopenia as compared with the cases in which the platelet count was more than 100,000 per cubic millimeter in the group in which hemorrhagic manifestations occurred. The Lee-White test of the coagulation time was of little help in an evaluation of the tendency to bleed in cases of cirrhosis, as is evident by the analysis of 40 cases in which it was performed (table 2).

SPLENIC ANEMIA [3]

We also reviewed a group of cases of splenic anemia, because of the constant association of hepatic cirrhosis in them. We analyzed the records in a series of 50

TABLE 3.—*Platelet Count in Cases of Splenic Anemia With and Without Bleeding*

Blood Platelet Count, per Cu. Mm.	Total Cases		With Bleeding		Without Bleeding	
	Number	Per Cent	Number	Per Cent	Number	Per Cent
Less than 50,000	1	2.0	1	2.6		
50,000 to 100,000	22	44.0	18	46.2	4	36.4
100,000 to 150,000	14	28.0	11	28.2	3	27.2
150,000 or more	13	26.0	9	23.0	4	36.4
Total	50	100.0	39	100.0	11	100.0
Mean count	126,000		119,000		150,000	

TABLE 4.—*Splenic Anemia: Relation of Platelet Count to Bleeding Time and Lee-White Coagulation Time*

Blood Platelet Count, per Cu. Mm.	Bleeding Time			Lee-White Coagulation Time		
		Time Elevated *			Time Elevated †	
	Cases	Cases	Per Cent	Cases	Cases	Per Cent
Less than 100,000	13	3	23.0	4	1	25.0
100,000 to 150,000	9	9	100.0	4	0	0.0
150,000 or more	6	0		1	0	
Total	28	12	42.9	9	1	11.1
Hemorrhagic manifestations	23	10	43.5	7	1	14.3
No hemorrhagic manifestations	5	2	40.0	2	0	

* Any value of more than three minutes was considered elevated.
† Any value of more than ten minutes was considered elevated.

cases in which platelet count was recorded prior to splenectomy (table 3). In 11 (22 per cent) bleeding had not occurred. In 4 of these 11 (36.4 per cent) there was definite thrombopenia; in 4 the platelet count was normal. In 39 cases a tendency to bleed was present. In 19 of these cases (48.8 per cent) definite thrombopenia was present, and in 1 the count was below the critical level. In 9 cases (23 per cent) in which some form of bleeding had occurred the platelet count was normal. In the cases of splenic anemia the bleeding was most frequently from the gastrointestinal tract, although it also occurred from the gums, nose and vagina and into the skin and the sclera of the eye. It is noteworthy that the percentage incidence of thrombopenia is definitely higher in the cases in which there was a hemorrhagic tendency than in those in which bleeding did not occur,

3. In this communication the term splenic anemia is applied to that group of conditions sometimes termed Banti's disease, in which there is a marked anemia and splenomegaly and associated leukopenia. In all of our cases hepatic cirrhosis was present.

although the contrast is less striking than it was in the cases of cirrhosis of the liver previously cited. In only 3 cases was a record made of the prothrombin time, and in every instance this was normal. In this group of cases, as in those of cirrhosis, an estimation of the bleeding time was an unreliable index of the bleeding tendency (table 4). This comment applies also to the Lee-White coagulation time (table 4), although it is apparent that these factors were estimated too infrequently to provide the basis for any deduction.

COMMENT

Thrombopenia occurred in a significant percentage of cases of splenic anemia. This is in accord with the observations of others. It is worthy of comment that in our cases of hepatic cirrhosis definite thrombopenia occurred in 17.5 per cent; although this incidence is less than half that in the cases of splenic anemia, it is significant. The fact that when the incidence of hemorrhagic phenomena is compared in regard to cirrhosis (58.8 per cent) and splenic anemia (78 per cent) it is greatest in the cases in which the incidence of thrombopenia is highest does not seem to us a chance observation.

King [4] in 1929 studied 100 cases of portal cirrhosis and found that in 72 a record of the number of blood platelets had been made. It was subnormal in 20 per cent. This figure compares with an incidence of thrombopenia of 17.5 per cent in our cases of hepatic cirrhosis. In King's series abnormal bleeding and clotting times were noted concurrently with a subnormal platelet count in only 2 cases. Howar [5] found a definite diminution of the platelet count in 50 per cent of a small series of cases of cirrhosis but found no constant relation between the reduction of the platelet count and an alteration in the bleeding time. Abrami [6] noted a tendency toward thrombopenia in hepatic disease. Alt and Swank [7] noted almost complete disappearance of thrombocytes with purpura in a case of catarrhal jaundice. Alt, Carroll and Doherty [8] noted a similar case in which severe hemorrhagic manifestations were present. Fellinger and Klima [9] observed thrombopenia in clinical cirrhosis of the liver. Experimental substantiation of these clinical observations occurs in the report of Higgins and Stasney,[10] who found that when cirrhosis of the liver was produced in rats by the administration of carbon tetrachloride the thrombocytes in the peripheral blood stream diminished and that when severe cirrhosis occurred the number of thrombocytes was reduced to almost a third of normal.

It therefore appears that the thrombopenia which is an accompaniment of severe hepatic disease in a significant percentage of cases is not an unimportant phenomenon. We have seen in the summaries of the cases reported and in the analysis of the group of cases studied that this thrombopenia appears to play some part in the tendency to bleed which often is manifest in these cases. Since the

4. King, R. B.: The Blood Picture in Portal Cirrhosis of the Liver: A Report Based on One Hundred Cases, New England J. Med. **200**:482-484 (March 7) 1929.

5. Howar, B. F.: Hematologic Studies in Liver Disease, J. Iowa M. Soc. **28**:148-150 (April) 1938.

6. Abrami, P.: Le purpura des hepatiques, Ann. de méd. **37**:71-79 (Jan.) 1935.

7. Alt, H. L., and Swank, R. L.: Thrombopenic Purpura Associated with Catarrhal Jaundice: Report of a Case, Ann. Int. Med. **10**:1049-1054, (Jan.) 1937.

8. Alt, H. L.; Carroll, H. B., and Doherty, C. C.: Thrombopenic Purpura Associated with Catarrhal Jaundice, Northwestern Univ. Bull., M. School **14**:183-186, 1940.

9. Fellinger, K., and Klima, R.: Lebercirrhose und Anämien, Ztschr. f. klin. Med. **126**: 547-567, 1934.

10. Higgins, G. M., and Stasney, J.: The Peripheral Blood in Experimental Cirrhosis of the Liver, Folia haemat. **54**:129-144 (Feb.) 1936.

only known function of the blood platelet is concerned with the mechanism of blood clotting, it is readily apparent that a considerable disturbance from normal of this constituent of blood may have important effects. For example, rupture of an esophageal varix would be an especially serious complication in a case in which the platelet count was less than 50,000, because there would be little if any tendency for a clot to form; even if the platelet count were between 50,000 and 100,000, the formation of a firm clot would be seriously impaired. Best and Taylor [11] suggested that perhaps one of the functions of the platelets in the mechanism of blood clotting is their liberation of the important substance prothrombase. Eagle [12] stated that the physiologic role of the platelets in coagulation is their enormous acceleration of the production of thrombin. Whether a platelet factor actually combines with prothrombin or merely accelerates a reaction which proceeds slowly even without it is not known. Consideration of the exact biochemical role which the blood platelets play is not within the purpose or scope of this paper. That the blood platelet is important and that a normal concentration is necessary in the maintenance of normal health is apparent when one considers such clinical manifestations of abnormal concentrations as thrombopenic purpura and its hemorrhagic complications. Since it is evident that a significant degree of thrombopenia coexists with severe hepatic disease in some cases, it is immediately apparent that this factor at times may modify seriously and complicate the hemorrhagic tendency, which has so long been a stumbling block in the care of patients who have severe hepatic damage. That the one factor of thrombopenia apparently can be the basis for a severe hemorrhagic tendency is suggested in case 1. It is well known that in serious hepatic damage associated with disturbance in the prothrombin level of the blood, adequate administration of vitamin K sometimes is ineffective in rectifying the lack of prothrombin. It has been suggested that this failure is due to an inability on the part of the severely damaged liver to utilize the vitamin in the synthesis of prothrombin. It is well to remember, however, that even though the administration of this vitamin brings about a normal state of prothrombin in the blood, there may still be the hazard of hemorrhage from other equally important associated factors. Fortunately, this problem does not confront one often in cases in which surgical intervention is needed. However, we feel that this study serves to emphasize that in cases of severe hepatic disease more than one factor may be at fault in bringing about an abnormal state of coagulability of the blood; it emphasizes the need to evaluate these cases from every standpoint and suggests that, although general understanding of the bleeding tendency in hepatic disease has been much improved in recent years, the problem is not solved completely. Undoubtedly other avenues of investigation must be explored before one can hope to reach a complete understanding of this complicated and important matter.

SUMMARY AND CONCLUSIONS

It is important to call attention to the possibility that factors other than the concentration of prothrombin may be of significance in explaining the aberrations from normal noted in the mechanism of coagulation of blood in cases of severe damage to the liver. Our attention was recently turned to the possibility that thrombopenia might be an important factor in explaining the severe hemorrhagic tendency sometimes encountered in hepatic disease. A series of 80 cases of hepatic

11. Best, C. H., and Taylor, N. B.: The Physiological Basis of Medical Practice: A University of Toronto Text in Applied Physiology, Baltimore, William Wood & Company, 1937.

12. Eagle, H.: Studies on Blood Coagulation: I. The Rôle of Prothrombin and of Platelets in the Formation of Thrombin, J. Gen. Physiol. **18**:531-545 (March 20) 1935.

cirrhosis was reviewed, and definite thrombopenia was found in 17.5 per cent. Although a definite hemorrhagic tendency was evident in many of these cases regardless of the level of the blood platelets, it was relatively twice as frequent when thrombopenia was associated. However, a hemorrhagic tendency is not exhibited in all cases of thrombopenia, for in 2 of a total of 14 cases of cirrhosis and thrombopenia bleeding of any kind did not occur.

The records in 50 cases of splenic anemia also were studied. The incidence of thrombopenia was higher than in the cases of cirrhosis, and the incidence of bleeding was increased correspondingly. In these cases, as in those of cirrhosis, the tendency to bleed was greater with a significant reduction in the level of thrombocytes.

We believe that the diminution of the blood platelets in severe hepatic disease of long standing is not a chance and unimportant finding. In our study we did not discover an explanation for this alteration, but we feel that in its presence the bleeding hazard is definitely increased. Our observations serve to emphasize the complexity of the important problem of bleeding in hepatic disease and suggest that further exploration of the various factors concerned will be necessary to clarify it.

The Mayo Clinic.

STUDIES IN SYPHILIS

I. REVIEW OF THE INCIDENCE OF SYPHILIS IN AUTOPSIES ON ADULTS

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Clinical investigations of the biology of syphilitic infection have been directed essentially to the elucidation of the problems of diagnosis, therapy and its complications, end results and serology. By its very nature, the clinical approach has been practically limited to the study of the disease in the viable host, and as a result many tangential issues have received no more than cursory and scattered attention. It is apparent that the coordination and correlation of the clinical aspects of the disease with the observations at autopsy will throw light on many problems which are still in the penumbra of knowledge. How frequently do persons with clinically diagnosed syphilis present morphologic evidence of syphilis at autopsy? What is the relationship between clinical cure and morphologic lesions at death? How often does a person with clinically diagnosed syphilis die as a direct result of his disease, and how often is the disease a contributory or a noncontributory factor in causing death? Is the distribution of the causes of death among persons with syphilis, apart from this disease, any different from that of the nonsyphilitic population? Of corollary interest, does syphilis confer any susceptibility or resistance to other diseases? What for instance, is the probability of death from cancer or from other morbid processes among syphilitic as compared with nonsyphilitic persons? Is there any correlation between serologic observations and morphologic evidence of syphilis at death? How does the longevity of the syphilitic person compare with that of the nonsyphilitic?

A stimulating paper by Moore [1] tersely summarized many unknowns in syphilology and indicates the range of our primary interest:

> In spite of 400 years of study, we still do not know the actual importance of syphilis as a cause of death. . . . To what extent . . . does death directly from syphilis masquerade under other diagnoses; or to what extent is syphilis an indirect cause of death from other conditions? . . .
>
> The modern necropsy studies of syphilitic patients, such as those of Warthin, provide no answers to these questions. Such studies, while revealing a very high incidence of lesions of syphilis, especially in aorta, heart, meninges and testes, provide no correlation between the clinical status and the necropsy findings, no information as to cause of death, and no data as to the kind and amount of treatment, if any, given during life. What is clearly here needed is a detailed study of both clinical and necropsy data in a very large series of patients,

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Since this paper was submitted, two reports in the series have been published: Black-Schaffer, B., and Rosahn, P. D.: Studies in Syphilis: II. Methods of Analysis of Yale Autopsy Protocols, Including a Code for the Punched Card Study of Syphilis, Yale J. Biol. & Med. **15**:575, 1943. Rosahn, P. D., and Black-Schaffer, B.: Studies in Syphilis: III. Mortality and Morbidity Findings in the Yale Autopsy Series, ibid. **15**:587, 1943.

1. Moore, J. E.: Unsolved Clinical Problems of Syphilology, Am. J. Syph., Gonor. & Ven. Dis. **23**:701, 1939.

to provide information as to the frequency with which patients recognized as syphilitic during life, either on clinical or laboratory grounds, showed lesions of syphilis at necropsy and what these lesions, if any, were; the frequency with which patients adequately studied during life with no discoverable evidence of syphilis showed such evidence at necropsy; the relationship of clinically or pathologically recognized syphilis to the final illness and the direct or indirect cause of death; the relationship of necropsy evidence of syphilis to treatment during life; and a dozen similar factors as yet unknown.

These and other related problems form the background for a survey now in progress. The basis for this study consists of 5,300 autopsies performed in the department of pathology at the Yale University School of Medicine since 1917. Supplementary and complementary information has been derived from a review of the pertinent literature. The present report constitutes the first paper in the series and is devoted to a critical review of the available literature on the incidence

TABLE 1.—*Incidence of Syphilis at Autopsy Among Persons Aged 20 and Over*

Author *	Country	Years	Number of Autopsies	Persons with Syphilis	
				Number	Per Cent
Herxheimer †	Germany	1906-1930	10,400	270	2.60
Bell [19]	U. S. A.	1910-1937	19,785	601	3.04
Gürich ‡	Germany	1914-1924	23,179	806	3.48
Hansteen §	Norway	1907-1925	11,376	515	4.53
Teodori [16]	Italy	1918-1935	7,673	371	4.84
Frates [17]	Italy	1928-1933	8,217	418	5.09
Melchior [18]	Denmark	1914-1920	4,594	245	5.30
Langer ‖	Germany	1906-1925	23,015	1,268	5.51
Guldberg [22]	Norway	1896-1930	8,235	481	5.84
Symmers [11]	U. S. A.	1906-1916	5,000	314	6.28
Nickel [20]	Germany	1907-1933	11,476	827	7.21
Ogden [12]	U. S. A.	1931-1938	5,408	418	7.73
Ophüls [7]	U. S. A.	1900-1923	2,492	280	11.24
Koppisch [9]	Porto Rico	1926-1938	665	75	11.30
Manohar [8]	India	1927-1934	2,721	431	15.84
Hala [6]	U. S. A.	1922	850	179	21.06
Warthin [5]	U. S. A.	1909-1929	1,675	494	29.49
Total (7 different countries)		1896-1938	146,761	7,993	5.45

* The symbols (†, ‡, § and ‖) refer to footnotes to the table. Superior figures refer to footnotes throughout the text.

† Herxheimer, J.: Syphilitische Veränderungen des Herzens und der Arterien, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1931, vol. 16, pt. 2.

‡ Gürich: Ueber die syphilitischen Organveränderungen die unter dem Sektionsmaterial der Jahre 1914-1924 angetroffen wurden, München. med. Wchnschr. **72**: 980, 1925.

§ Hansteen, cited by Guldberg.[22]

‖ Langer, E.: Die Häufigkeit der luetischen Organveränderungen, insbesondere der Aortitis luetica, München. med. Wchnschr. **73**: 1782, 1926.

of syphilitic infection in adults as determined by various autopsy studies. Other reports bearing on the general problem will follow.

The literature on the pathologic changes of syphilis contains no comparative or summated analysis of the isolated surveys of autopsy populations that have appeared from time to time. Many authors have directed their attention to specific types of syphilitic lesions, and as a result the scope of their studies has been limited to particular organ systems or to special tissue reactions. Comparatively few investigators have been concerned with the incidence of syphilis at autopsy in its broadest, all-inclusive aspects, and many of their studies have appeared in foreign publications not readily accessible in America.

It is the principal purpose of this paper, therefore, to collate and evaluate the available reports on the frequency of morphologically diagnosed syphilis in autopsy populations. The review to be presented is concerned with syphilis in its acquired form, and for convenience in analysis the autopsy populations have been limited to persons aged 20 and over. Wherever necessary published reports have been recast to give the incidence of syphilis by decades beginning with the

age of 20, this revision, however, in no way altering the factual data presented by the author. It is admitted at the outset that there may be included a certain small number of syphilitic persons over 20 whose infection was congenital, but these are adequately counterbalanced by the exclusion of persons under 20, some of whom no doubt had acquired syphilis. At any rate, the populations under consideration are large enough to reduce effectively any error introduced by taking the age of 20 as the arbitrary lower limit of acquired syphilis.

Table 1 presents a summary of available reports on the incidence of syphilitic lesions in autopsy populations. The data of this table are graphically depicted in chart 1. Four countries of Continental Europe, one in Asia, one West Indian island and the United States are represented. The frequency of syphilitic changes encountered at autopsy among persons over 20 years of age varies from a low

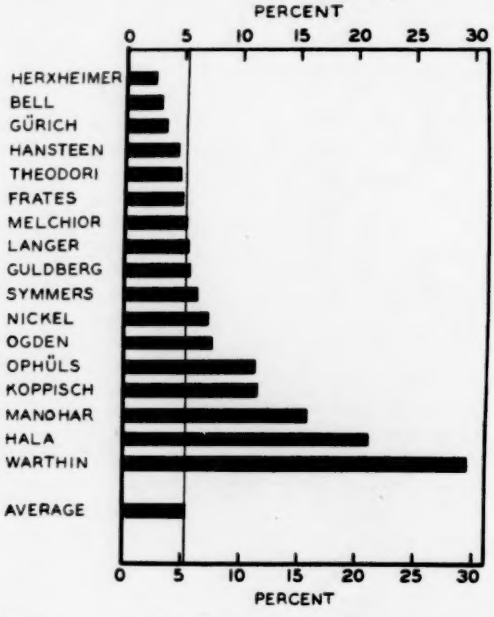

Chart 1.—Incidence of syphilis at autopsy among persons over 20 years of age.

of 2.6 per cent to a high of 29.5 per cent. The average for all of the seventeen reports presented in the table is 8.8 per cent. This average, however, gives equal weight to each of the reports regardless of the number of observations on which it was based. An alternative average value is one based on the entire summated autopsy population in the seventeen reported series. Of a total of 146,761 persons, 7,993, or 5.45 per cent, were observed to be syphilitic at autopsy.

Other reports on the incidence of syphilitic lesions at autopsy are available, but for the stated reasons they were not incorporated in table 1. Brines [2] studied 618 routine autopsies performed in 1934 at the City of Detroit Receiving Hospital, where 36 per cent of the patients admitted were Negroes. He found 54 instances of gross and microscopic syphilis, an incidence of 8.7 per cent, but failed

2. Brines, A. O.: Laboratory Diagnosis of Syphilis, in Papers of the Michigan Academy of Science, Arts and Letters, Ann Arbor, Mich., University of Michigan Press, 1936, vol. 21, p. 561.

to give the age and sex composition of the autopsy group. Turnbull [3] studied more than 7,000 necropsies performed in London between 1908 and 1913 and found that approximately 4 per cent had disclosed lesions of acquired syphilis. Incomplete data prevent an exact computation of incidence. Pohlen [4] reviewed 8,182 autopsies performed in Magdeburg between 1928 and 1936. Of the subjects studied, 557, or 6.8 per cent, had morphologic evidence of syphilis. This figure includes both those with congenital and those with acquired lesions, who cannot be readily segregated on the basis of the data as given.

Twelve of the seventeen reports listed in table 1 showed an incidence of syphilis of less than 8 per cent, while only five authors gave an incidence higher than 11 per cent. A comparison of individual results shows a striking variation between those of Warthin,[5] Hala,[6] Ophüls,[7] Manohar [8] and Koppisch,[9] on the one hand, and the remaining authors, on the other. If we place the summated observations of these five authors in one classification and compare their results with those of the remaining authors, the difference is striking:

Authors	Autopsies, Number	Instances of Syphilis	
		Number	Per Cent
Warthin, Hala, Ophüls, Manohar and Koppisch....	8,403	1,459	17.36
12 others	138,358	6,534	4.72

It is, moreover, apparent that as regards reports emanating from the United States, there are two clearcut and distinct schools of opinion. The first school, represented by Bell,[10] Symmers [11] and Ogden,[12] reported 1,333 instances of syphilis among 30,193 autopsies on persons aged 20 and over, a frequency of 4.4 per cent. Warthin,[5] Hala [6] and Ophüls,[7] representing the second school, found 953 cases of syphilis in an autopsy population of 5,017, an incidence of 19 per cent. The marked disparity between these two sets of results represents one of the outstanding problems of modern syphilology.

It is conceivable that the differences are real and characteristic of the different populations under investigation. On this basis syphilis was actually ten times as frequent in the population studied by Warthin as in that surveyed by Bell. If it is true that treatment effectively eliminates all morphologic traces of syphilis, the variable incidence might be explained by differences in the availability and intensity of syphilotherapy in the several communities forming the reservoirs for the different autopsy populations. Information on this point is outside the range of the present report, but other considerations suggest that the entire explanation

3. Turnbull, H. M.: Alterations in Arterial Structure and Their Relation to Syphilis, Quart. J. Med. **8**:201, 1914-1915.

4. Pohlen, K.: Ueber die Häufigkeit der Syphilis und der syphilitischen Folgezustände nach dem klinischen und pathologischen Gefund, Dermat. Wchnschr. **105**:1469, 1937.

5. Warthin, A. S.: The New Pathology of Syphilis, Am. J. Syph. **2**:425, 1918; The Role of Syphilis in the Etiology of Angina Pectoris, Coronary Arteriosclerosis and Thrombosis, and of Sudden Cardiac Death, Am. Heart J. **6**:163, 1930.

6. Hala, W. W.: Incidence of Syphilis, Am. J. Syph. **6**:616, 1922.

7. Ophüls, W.: A Statistical Survey of Three Thousand Autopsies, Stanford University Pub., Univ. Series, M. Sc. **1**:234, 1926.

8. Manohar, K. D.: Incidence of Syphilis, Indian J. Ven. Dis. **1**:9, 1935.

9. Koppisch, E.: La siflis en Puerto Rico: Estudio basado en la revision de 1000 autopsias consecutivas (informe preliminas), Bol. Asoc. méd. de Puerto Rico **31**:160, 1939.

10. Bell, E. T.: Frequency with Which Syphilitic Lesions Are Encountered in Postmortem Examinations, Arch. Path. **26**:839 (Oct.) 1938.

11. Symmers, D.: Anatomic Lesions in Late Acquired Syphilis, J. A. M. A. **66**:1457 (May 6) 1916.

12. Ogden, M. A.: Aneurysm of the Aorta, Urol. & Cutan. Rev. **44**:731, 1940.

does not lie in this direction. In the first place, the primary premise, that treatment effectively eradicates the morphologic changes of syphilis, is a problem yet to be settled. In the second place, even if this premise were accepted, the necessary conclusion that syphilis is treated more than four times as effectively in New York, where Symmers found an incidence of 6.3 per cent, than in Michigan, where Warthin reported a 29.5 per cent frequency, would appear untenable.

Other factors, such as variability in economic status, in race, in age and in sex distribution of the subjects comprising the different autopsy populations, are of importance, and these will be discussed in subsequent paragraphs. A critical analysis of the diagnostic criteria employed by the different authors may also throw some light on their widely divergent findings.

RACE

It is well known that syphilis is much more frequent in the American Negro than in the white race. Keidel and Moore,[13] among 5,000 patients admitted to the medical ward of Johns Hopkins Hospital, found positive Wassermann reactions of the blood in 7.6 per cent of the white persons and in 22.9 per cent of the Negroes. Among 4,000 discharged medical patients, syphilis was diagnosed in 9.7 per cent of the white persons and in 25.4 per cent of the Negroes. Other authors, notably Turner [14] and Paullin, Davison and Wood,[15] have reported comparable results. However, it is not possible to explain the divergent results summarized in table 1 entirely on the basis of the racial composition of the different autopsy populations. All of the European patients were adult Caucasians, and this is true also of Warthin's group. The population studied by Ophüls was composed of 91.3 per cent white persons, no attempt having been made to correlate race with morphologic changes, because of the small number of Negroes. Hala and Symmers made no mention of the racial composition of their groups. In Koppisch's series the incidence of syphilis among white persons was 8.6 per cent, as contrasted to an incidence among mulattoes of 13.8 per cent and among Negroes of 16.9 per cent. These last two groups comprised 37.5 per cent of the population and contributed 52 per cent of the syphilitic subjects. It is thus seen that the relatively high incidence of syphilis reported by Koppisch can be accounted for at least in part by the inclusion of a large number of mulattoes and Negroes, in whom the disease is more frequent than in the white race. Ogden's autopsy group consisted of 2,280 white persons, 89 of whom had syphilis, an incidence of 4 per cent, and 3,128 Negroes, 329 of whom had anatomic syphilis, an incidence of 10.5 per cent. Manohar's observations will receive more detailed discussion later. The cardinal point with regard to race is that, although syphilis is demonstrably more frequent in the Negro than in the white person, the racial composition of the different populations is alone insufficient to explain the diverse results. Warthin, reporting the highest incidence, studied a population consisting solely of white persons.

Manohar requires special consideration because he was dealing with natives of India, a racial group not comparable to any investigated by the European and American authors. His series consists of two groups. The first was composed of 882 persons autopsied at the Grant Medical School, in Bombay. Syphilis was

13. Keidel, A., and Moore, J. E.: The Wassermann Reaction in the Johns Hopkins Hospital, Bull. Johns Hopkins Hosp. **34**:16, 1923.

14. Turner, T. B.: The Race and Sex Distribution of the Lesions of Syphilis in Ten Thousand Cases, Bull. Johns Hopkins Hosp. **46**:159, 1930.

15. Paullin, J. E.; Davison, H. M., and Wood, R. H.: The Incidence of Syphilitic Infection Among the Negroes in the South, Boston M. & S. J. **197**:345, 1927.

diagnosed at autopsy in 20.7 per cent of these. The second comprised 1,839 persons autopsied by police surgeons, among whom 13.1 per cent had lesions of syphilis. In the latter group only the principle cause of death was investigated, while the first was thoroughly studied by complete gross examinations. This author recorded the remarkable observation that 49 per cent of the persons autopsied at the medical school had syphilitic lesions of the heart, generally recognizable on gross examination. This observation, which is at complete variance with the entire literature, is explicable only on the basis of the author's diagnostic critera. These, however, he fails to describe.

SOCIAL AND ECONOMIC STATUS

It is difficult to evaluate the social and economic status of the autopsy populations studied by the various authors listed in table 1. Most of the reports are

TABLE 2.—*Frequency of Syphilitic Lesions in Men and in Women as Diagnosed at Autopsy by Five Different Investigators*

Author	No. of Autopsies	Men, Total		Women, Total		Persons with Syphilis			
						Men		Women	
		No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent
Bell	19,785	13,106	66.2	6,682	33.8	480	3.6	121	1.8
Frates	8,217	5,217	63.5	3,000	36.5	314	6.0	104	3.4
Koppisch	665	494	74.3	171	25.7	65	11.8	10	5.8
Melchior	4,594	2,482	54.0	2,112	46.0	171	6.9	74	3.5
Teodori	7,673	4,222	55.0	3,451	45.0	300	7.1	124	3.5
Total	40,934	25,518	62.3	15,416	37.7	1,330	5.2	433	2.8

TABLE 3.—*Frequency of Syphilitic Lesions in Men and in Women as Diagnosed in Five Different Investigators (Observed and Expected Values Summated from Table 2)*

Sex	Syphilitic		Nonsyphilitic		Total
	Observed	Expected	Observed	Expected	
Men	1,330	1,099	24,188	24,419	25,518
Women	433	664	14,983	14,752	15,416
Total	1,763	1,763	39,171	39,171	40,934

based on persons in the general category "city hospital patients." There were private patients in the series studied by Bell and in the populations analyzed by several of the German and Scandinavian authors. From this viewpoint alone, the 29.5 per cent incidence of syphilis in Warthin's group of "private patients" is noteworthy.

SEX

Only five of the authors named in table 1 have published sufficient information to relate sex to acquired syphilis demonstrable by lesions at autopsy. Their reports are summated in tables 2 and 3. Of 40,934 autopsied persons over 20, 62.3 per cent were men and 37.7 per cent women. Among these, 1,763 had evidence of syphilitic infection, of whom 75.4 per cent were men and 24.6 per cent were women. Thus, whereas approximately three fifths of the autopsy population were men, men accounted for three fourths of the cases of syphilis. Analysis by the chi-square test of homogeneity (table 3) indicates a statistically significant difference between these values. It can be concluded that a higher proportion of men and a lower

proportion of women showed evidence of syphilis at autopsy than could be expected on the basis of the proportions of the sexes in the combined populations. Syphilis was diagnosed in 5.2 per cent of the male population, a significantly higher percentage than that observed among women, i. e., 2.8 per cent.

Each of the five authors presenting data on the sex incidence of syphilis at autopsy reported a frequency among males approximately twice that observed among females. Unfortunately the reports of four authors, namely, Ophüls, Manohar, Hala and Warthin, who found the highest incidence of syphilis, do not lend themselves to an analysis of the sex distribution either of their total autopsy population or of their syphilitic population. A critical evaluation of their material in the light of this general conclusion with regard to sex is therefore not feasible.

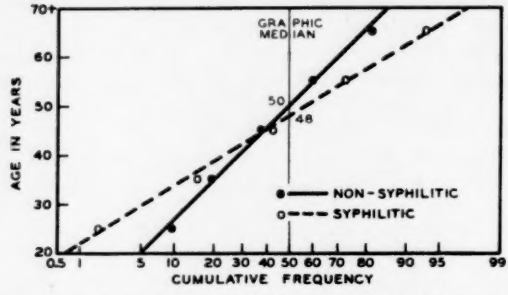

Chart 2.—Age of men with and without syphilitic lesions at autopsy.

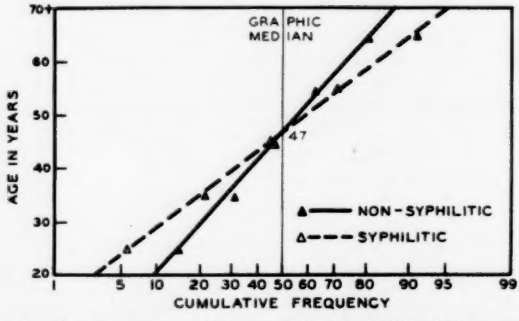

Chart 3.—Age of women with and without syphilitic lesions at autopsy.

It is, however, justifiable to conclude that the varied incidence of syphilis encountered by the different observers cannot be wholly the result of a preponderance of males in their autopsy populations.

AGE

The data presented by Teodori,[16] Bell,[10] Frates,[17] Melchior[18] and Koppisch[9] are the only published reports sufficiently exhaustive to permit of a summated

16. Teodori, U.: Rilievi statistici concernenti la sifilide nel materiale autoptico dell'Instituto di Anatomia Patologica di Firenze dal 1918 al 1935 con rilievi comparativi sulla frequenza dei tumori maligni e della tubercolosi, Dermosifilografo **13**:143, 1938.

17. Frates, A.: Considerazioni statistiche sulla sifilide nelle prime 10,000 autopsie del'Instituto di Anatomia Pathologica della R. Università di Milano, Clin. med. ital. **65**:1015, 1934.

18. Melchior, L.: Om sektionsfund og dodsaarsager hos patienter med erhvervet syfilis, Ugesk. f. læger **84**:1351, 1922.

analysis of the incidence of syphilitic lesions at autopsy in relation to age at death. The findings of these five authors form the basis for the following discussion of age and syphilis in men at autopsy. The last author's data are not included in the consideration of age and syphilis in women because of the small number of women in his series. The summated data are presented in table 4 and charts 2, 3 and 4. The figures were drawn on arithmetical probability paper and show the cumulative percentages by decades. A normal frequency distribution when charted on this type of paper is represented by a straight line. Deviation from a straight line is indicative of corresponding deviation from a normal distribution. The median is easily determined graphically by the intersection of the 50 per cent ordinate with the frequency curve. The slope of the frequency line indicates the degree of variability of the data: the steeper the slope, the greater the variability (Schrek [19]).

The mean age (chart 4) of nonsyphilitic men over 20 was 54 ± 0.14 years, a value significantly higher than that found for nonsyphilitic women, 52.09 ± 0.23

TABLE 4.—*Analysis of Sex Distribution of Persons With and Without Syphilitic Lesions at Autopsy*

Age	Nonsyphilitic			Syphilitic		
	Number	Per Cent of Total	Cumulative per Cent	Number	Per Cent of Total	Cumulative per Cent
			Men *			
20-29	2,229	9.2	9.2	22	1.7	1.7
30-39	2,356	9.7	18.9	174	13.4	15.1
40-49	4,459	18.4	37.4	358	27.7	42.8
50-59	5,373	22.2	59.6	381	29.5	72.3
60-69	5,384	22.3	81.9	272	21.1	93.3
70+	4,391	18.2	100.0	86	6.7	100.0
Total	24,192	100.0		1,292	100.0	
			Women †			
20-29	2,191	14.8	14.8	21	5.3	5.3
30-39	2,297	15.5	30.2	62	15.5	20.8
40-49	2,384	16.1	46.3	95	23.8	44.5
50-59	2,383	16.1	62.3	106	26.5	71.0
60-69	2,716	18.3	80.6	80	20.0	91.0
70+	2,874	19.4	100.0	36	9.0	100.0
Total	14,845	100.0		400	100.0	

* The data are based on the reports of Bell, Frates, Koppisch, Melchior and Teodori.
† The data are based on the reports of Bell, Frates, Melchior and Teodori.

years. The mean age of the men with syphilis was 52.53 ± 0.36 years, which is significantly lower than that of the nonsyphilitic men. In contrast to this finding, the mean age of syphilitic women was 51.95 ± 1.01 years, actually no different from the mean value for the nonsyphilitic women. In these cumulative observations it appears that the average span of life of the syphilitic man was shortened by about two years, as compared with that of the nonsyphilitic man, although the woman with syphilis had an average duration of life no shorter than her nonsyphilitic sister. Sex apparently exerted no significant influence on the average age at death of the syphilitic person, since both men and women with syphilis had a mean age of about 52 years.

Great care must be exercised in drawing conclusions from the mean age at death, because such values are easily affected by variations in the age distribution of different groups. For this reason the analysis shown in table 4 and charts 2 and 3 is presented. About 9 per cent of the deaths in the nonsyphilitic male population over 20 years of age occurred during the third decade of life, as compared

19. Schrek, R.: Further Quantitative Methods for the Study of Transplantable Tumors: The Growth of R39 Sarcoma and Brown-Pearce Carcinoma, Am. J. Cancer **28**:345, 1936.

with less than 2 per cent of the deaths among syphilitic men. Approximately 50 per cent of the deaths in the nonsyphilitic group occurred between 30 and 59 years of age, while 70 per cent of the syphilitic deaths took place in this age class. Finally, about 20 per cent of the nonsyphilitic men survived beyond the age of 70, in contrast to less than 7 per cent of those with syphilis.

A similar analysis of the data for women gives essentially similar results. About 15 per cent of the deaths among nonsyphilitic women took place in the third decade of life, as compared with only 5 per cent of the syphilitic deaths. Approximately half of the nonsyphilitic women died between 30 and 60 years of age, as compared with two thirds of the syphilitic women. Moreover, about 20 per cent of the nonsyphilitic women survived beyond the age of 70, in contrast to only 9 per cent of the syphilitic women.

It is not our intent that these curves be interpreted as being typical of syphilis in this country. A composite curve was drawn instead of individual curves for each author in order to smooth the irregularities that would appear in the limited observations in the individual reports. These composite curves should be compared with each other as regards syphilitic and nonsyphilitic persons. From this viewpoint, and in the combined experience of the authors cited, the syphilitic man

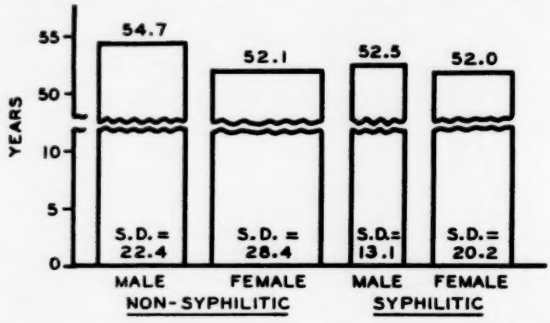

Chart 4.—Mean age and standard deviation for men and women with and without lesions of syphilis at autopsy. *S. D.* indicates standard deviation.

living into the forties and the syphilitic woman living into the fifties had a shorter life span than their nonsyphilitic brother and sister. It should be noted that each of the curves in charts 2 and 3 is represented by a straight line, indicating a normal frequency distribution.

One other observation with regard to age is of significance. This refers to the degree of variability of the frequency distributions for the syphilitic and nonsyphilitic men and women. In charts 2 and 3 the slope of the curve indicates variability; the steeper the slope the greater the variability. In chart 4 variability is proportional to the width of the bars. In both sexes the age distribution of the syphilitic group is less variable than that of the nonsyphilitic group, and this difference is highly significant. (The standard deviation equals 22.4 ± 0.10 for nonsyphilitic men and 13.07 ± 0.27 for syphilitic men, the difference being 9.33 ± 0.27, and t, 35. The standard deviation equals 28.4 ± 0.16 for nonsyphilitic women and 20.2 ± 0.23 for syphilitic women, the difference being 8.2 ± 0.28, and t, 30.) The extremes of age between 20 and 70 are lopped off in the syphilitic groups as compared with the nonsyphilitic. Fewer young and fewer old subjects are found in the syphilitic than in the nonsyphilitic population.

The incidence of syphilis diagnosed at autopsy in relation to age and sex is shown in table 5. The highest incidence of syphilis occurred among men in the fifth decade and among women in the sixth decade, but in each decade syphilis was more frequent among men than among women. A possible but completely improbable explanation for the high incidence of syphilis in Warthin's, Hala's and Ophüls' populations is here indicated. If their autopsy populations were composed entirely of Negro men aged 40 to 50, a plausible explanation for the high incidence of syphilis which they reported might be offered. There is internal evidence in their publications, however, to discredit this hypothesis, and other explanations must therefore be sought.

DIAGNOSTIC CRITERIA

It is generally recognized that the criteria for the pathologic diagnosis of syphilis are not definitive. Before the advent of Warthin's "The New Pathology of Syphilis" a relative uniformity of criteria did exist. These criteria were and still are to be found in the standard textbooks here and abroad. Outside of the United States and Canada, Warthin's influence has failed to make the impression which, on this continent at any rate, has resulted in the broadening of the pathologic

TABLE 5.—*Incidence of Syphilitic Lesions at Autopsy in Men and in Women According to Age, by Decades (Summated from Reports of Bell, Frates, Koppisch, Melchior and Teodori)*

	Total Number		Syphilitic Persons			
			Number		Per Cent	
Age	Men	Women	Men	Women	Men	Women
20-29	2,251	2,212	22	21	0.98	0.94
30-39	2,529	2,359	173	62	6.84	2.62
40-49	4,817	2,479	358	95	7.43	3.83
50-59	5,754	2,489	381	106	6.62	4.26
60-69	5,656	2,796	272	80	4.80	2.86
70+	4,477	2,910	86	36	1.92	1.24
Total	25,484	15,245	1,292	400	5.07	2.62

concept of syphilis. This influence is more readily appreciated when the reports on lesions of individual organs, such as the stomach, testicle, kidney, liver and adrenal glands, are considered than when the more general reports, such as those of table 1, are reviewed. It must, however, be stated that before Warthin's publications appeared, the specific nature of the syphilitic lesion was the subject of much controversy and in fact was the very basis which made Warthin's interpretation possible.

Because of the paucity of comparable anatomic studies, and the total lack of uniformity of criteria, the entire subject of the pathology of syphilis is a maze in which both the expert and the not-so-expert are frequently lost. When the incidence of syphilis of the liver in comparable populations ranges from 3.3 per cent to 33.4 per cent and when one author designates all hepatic syphilis as hepar lobatum, while another diagnoses only 33 per cent as such, it is obvious that complete confusion in terminology and interpretation of lesions exists. It thus becomes apparent that of primary importance in an evaluation of statistics of this type are the criteria followed by the different observers. Here one finds sufficient variability to account in large part for the divergent results.

Warthin [5] stated:

> The pathologic diagnosis of syphilis is essentially microscopic. Only in a relatively small number of cases are the gross lesions . . . typical enough to be recognized by the naked eye. A negative diagnosis of syphilis cannot be given with any certainty without a routine

microscopic examination of all organs and tissues, but particularly of the left ventricular wall, the aorta, both its arch and abdominal portion, the testes, pancreas and adrenals. . . .

The new pathology of syphilis is based upon the demonstration that the essential tissue lesion of either late or latent syphilis is an irritative or inflammatory process, usually mild in degree, characterized by lymphocytic and plasma cell infiltrations in the stroma particularly about the blood vessels and lymphatics, slight tissue proliferation, eventually fibrosis, and atrophy or degeneration of the parenchyma.

This concept is in direct contrast to that of Nickel,[20] who is representative of many of the authors listed in table 1. Nickel's criteria may be freely translated as follows:

Only definite anatomic syphilis, i. e., syphilitic vascular disease, syphilis of the central nervous system, syphilis of the bone, gumma and interstitial hepatitis of the newborn, was included. Presumptive evidence of syphilis was not considered, i. e., orchitis fibrosa, cicatricial atrophy of the tongue and so-called syphilitic cirrhosis, nor was a positive Wassermann reaction.

Nickel specifically disregarded orchitis fibrosa, lingua glabia and "so-called syphilitic cirrhosis" of the liver, nor did he mention changes in the pancreas and adrenals, as did Warthin. The latter also emphasized testicular fibrosis, and, in fact, Weller,[21] who was for many years associated with Warthin, made the following statement: "In our opinion, testicular lesions rank second only to those of the aorta as to value in recognition of latent (nongummatous) visceral syphilis." The contrast between Warthin and Nickel is readily apparent and is so sharply drawn that their conclusions cannot be fairly compared.

Symmers employed essentially the same criteria as Nickel but differed from him in the interpretation of specific lesions. For example, Symmers found that 33.4 per cent of his syphilitic subjects presented hepatic syphilis of both the hepar lobatum type and the cirrhotic form, while Nickel specifically excluded from his series subjects with so-called syphilitic cirrhosis. Moreover, Symmers included subjects with the "presumptive changes of syphilis," such as orchitis fibrosa and lingua glabia, in his series. In spite of this, it is noteworthy that there is no significant difference between the 7 per cent incidence reported by Nickel and the 6 per cent observed by Symmers.

Hala, apparently a disciple of Warthin, accepted as syphilitic any subject to whom two of the following criteria applied: (1) a clinical history of antecedent infection or clinical evidence of existing syphilis, (2) a positive Wassermann reaction, (3) the observation of typical gross lesions at autopsy and (4) histologic evidence of syphilis.

It is evident that the first two criteria are not anatomic, and since the number of subjects admitted to the series on this basis is not stated, the comparative value of the entire work is placed in jeopardy. Moreover, the freedom of action which the four criteria gives to the author is evidenced by the statement that "subpleural aggregations of small round cells (miliary gummata?)" were noted in a considerable number of persons with syphilis, all of whom had pulmonary tuberculosis and the large majority of whom died of tuberculosis.

Frates included not only persons with anatomic lesions but those with a positive Wassermann reaction or a clinical history of infection. However, these two groups are so well differentiated that it was possible to recalculate the author's findings and incorporate in table 1 only those cases in which there were definite anatomic lesions of syphilis.

20. Nickel, H.: Statistische Untersuchungen über die Häufigkeit der Lues am Obductionsmaterial, Klin. Wchnschr. **15**:121, 1936.

21. Weller, C. V.: The Visceral Pathology in Haitian Treponematosis, Am. J. Syph., Gonor. & Ven. Dis. **21**:357, 1937.

While Ophüls did not enumerate criteria in a formal statement, one may deduce them from his paper. For example, he included a subject with "myocardial syphilis on the basis of clinical history and course." He included another with chronic diffuse interstitial inflammation of pulmonary tissue with cor pulmonali, designated as syphilitic. Twenty per cent of Ophüls' syphilitic patients had syphilitic hepatic disease, in contrast to Warthin's 30 per cent and Nickel's 4.23 per cent. Ophüls also included patients with orchitis fibrosa but added, "They may be syphilitic." The remainder of the authors followed in general the criteria described by Nickel.

The reports show considerable variation with respect to the routine use of microscopic examination of tissues, or of gross examination alone, in the anatomic diagnosis of syphilis. There is, however, compelling evidence that this variation is less important in accounting for the difference in frequency rates than is the variability in diagnostic criteria. Among authors relying entirely or almost entirely on gross examination in reaching a diagnosis of syphilis are Teodori, Frates, Symmers, Manohar and Ophüls. The first three reported a frequency of 4.8 per cent, 5.1 per cent and 6.3 per cent, respectively. These are all comparable results. The last two recorded rates two and three times as great, that is, 15.8 per cent and 11.2 per cent. It appears from these reports that there is distinct lack of uniformity in the interpretation of the gross tissue changes produced by syphilis.

The same variability in diagnostic criteria is apparent in the reports based on microscopic evidence of syphilis. These include the reports of Guldberg [22] (5.8 per cent), Koppisch (11.3 per cent), Hala (21.1 per cent) and Warthin (29.5 per cent). The first of these authors found no greater incidence of syphilis through the study of routine histologic preparations than did Teodori, Frates or Symmers, all of whom relied predominantly on gross examination alone. The disparity between Guldberg's observations, on the one hand and Warthin's, on the other, is so striking as to suggest that it results not so much from a real difference in the incidence of syphilis in the two populations as from significant differences in the diagnostic criteria followed by the two investigators.

The conclusion is warranted that there is a clear need for a restatement of the morphologic changes, both gross and microscopic, which result from syphilitic infection. This is especially true with regard to the histologic alterations described by Warthin as definitive, and this aspect of the problem we plan to pursue in a future study. Precise evaluation of the anatomic changes of syphilis in terms of morbidity and mortality will depend primarily on the standardization of diagnostic criteria and on the general adoption of a unform nomenclature.

SUMMARY

A critical review of the available literature on the incidence of syphilitic infection in adults as determined by various autopsy studies is presented.

The frequency of syphilitic changes encountered at autopsy among persons over 20 years of age varied from a low of 2.6 per cent to a high of 29.5 per cent. The average for seventeen different reports was 8.8 per cent. The average based on the summated autopsy populations of the seventeen reports was 5.5 per cent.

Although syphilis was demonstrably more frequent in the Negro than in the white race, the racial composition of the different populations did not appear sufficient to account for the diverse results.

22. Guldberg, G.: Ueber Sektionsbefunde bei Syphilitikern, Arch. f. Dermat. u. Syph. **166**:730, 1932.

Exact information on the social and economic status of the several populations was lacking, but this status did not appear to play an important role in explaining the widely divergent findings.

A higher proportion of men and a lower proportion of women showed evidence of syphilis at autopsy than could be expected on the basis of the proportions of the sexes in the combined populations. The mean age of the men over 20 with syphilis in reports giving age and sex data was 52.1 years, or one and a half years younger than the mean age for nonsyphilitic men. This difference was significant. Women over 20 years of age with syphilis had an average age of 52 years, essentially the same as the mean age of the nonsyphilitic women. Only 7 per cent of the syphilitic men and 9 per cent of the syphilitic women survived the age of 70, in contrast to 20 per cent of the nonsyphilitic men and women. The highest incidence of syphilis occurred among men in the fifth decade and among women in the sixth decade, but in each decade syphilis was more frequent among men than among women. It could not be conclusively demonstrated that these findings with respect to age and sex were responsible for the widely divergent estimates of the incidence of syphilis at autopsy.

The great variability in the diagnostic criteria, both gross and microscopic, employed by different observers was appraised, and the need for uniformity of nomenclature and standardization of criteria was stressed. It was suggested that the major factor accounting for the great variability in the frequency of syphilitic lesions encountered at autopsy was precisely this lack of uniformity in the diagnostic criteria employed by the several investigators.

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NITROGEN EQUILIBRIUM AND REGENERATION OF SERUM PROTEIN

FOLLOWING INTRAVENOUS USE OF AMINO ACIDS

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Attention to nitrogen balance and the level of the blood proteins has of late years come to be recognized as an important part of preoperative and postoperative care [1] in cases of diseases of the liver [2] and biliary tract,[3] of severe burns [4] and of shock.[5] A variety of substances have been used as sources of nitrogen. In shock, the necessity of obtaining immediate increase in osmotic pressure of the serum to prevent hemoconcentration makes human plasma and serum of undisputed importance, since simply by giving them one places proteins in circulation. The protein is in addition available for use by the body for maintaining nitrogen equilibrium and building new serum protein. The cost of collection and preparation of human plasma and serum is considerable, and for this reason Wangensteen and his co-wokers [6] have attempted to use beef plasma as a substitute, with some degree of success. Solutions of hydrolyzed casein may also be prepared relatively cheaply, and since they are capable of being metabolized by the body [7] and furnish material with which serum proteins may be built, they may be used to advantage as a source of nitrogen. But because amino acids exert little if any osmotic pressure in solution, they obviously cannot replace whole blood or serum when an immediate effect on blood volume is required and are to be regarded as easily usable sources of nitrogen.

Elman and Weiner [8] have shown that plasma administered intravenously replenishes circulating proteins, but they stated that it must be completely broken down into simple amino acids and subsequently resynthesized before utilization. For this reason, they expressed the belief that amino acids resulting from the

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1. (*a*) Jones, C. M., and Eaton, F. B.: Postoperative Nutritional Edema, Arch. Surg. **27**:159 (July) 1933. (*b*) Stengel, A., Jr., and Ravdin, I. S.: The Maintenance of Nutrition in Surgical Patients, with a Description of the Orojejunal Method of Feeding, Surgery **4**:511, 1939. (*c*) Ravdin, I. S.; Stengel, A., Jr., and Prushankin, M.: The Control of Hypoproteinemia in Surgical Patients, J. A. M. A. **114**:107 (Jan. 13) 1940.

2. Ravdin, I. S.: The Protection of the Liver from Injury, Surgery **8**:204, 1940.

3. Jones, C. M.: Treatment of Biliary-Tract Disease, New England J. Med. **224**:509, 1941.

4. (*a*) Elman, R.: The Therapeutic Significance of Plasma Protein Replacement in Severe Burns, J. A. M. A. **116**:213 (Jan. 18) 1941. (*b*) McClure, R. D.: The Treatment of a Patient with Severe Burns, ibid. **113**:1809 (Nov. 11) 1939.

5. Bond, D. D., and Wright, D. G.: Treatment of Hemorrhage and Traumatic Shock by Intravenous Use of Lyophile Serum, Ann. Surg. **107**:500, 1938.

6. Wangensteen, O. H.; Hall, H.; Kremen, A., and Stevens, B.: Intravenous Administration of Bovine and Human Plasma to Man: Proof of Utilization, Proc. Soc. Exper. Biol. & Med. **43**:616, 1940.

7. Shohl, A. T.; Butler, A. M.; Blackfan, K. D., and MacLachlan, E.: Nitrogen Metabolism During the Oral and Parenteral Administration of the Amino Acids of Hydrolyzed Casein, J. Pediat. **15**:469, 1939.

8. Elman, R., and Weiner, D. O.: Intravenous Alimentation, J. A. M. A. **112**:796 (March 4) 1939.

hydrolysis of casein constitute at least as good material for building proteins as whole serum or plasma. Recently, Madden and co-workers [9] have shown experimentally that casein digests are utilized for producing new plasma protein in dogs made hypoproteinemic by plasmapheresis. With a suitable casein digest, the same response was elicited by either intravenous or oral administration, and nitrogen balance was maintained for considerable periods. Since the initial report of Elman and Weiner [8] on the use of hydrolyzed casein as a substance suitable for intravenous use in human beings, many other investigators [10] have contributed to the literature on the subject.

For the past year and a half, the effects of the use of solutions of amino acids on a variety of hypoproteinemic states and on maintenance of nitrogen balance have been studied in this hospital. The substance of this report is based mainly on the results obtained in 5 of a group of 20 patients who received amino acids intravenously. These 5 were studied in sufficient detail to permit drawing conclusions concerning their ability to use the amino acids for maintenance of nitrogen balance or to regenerate serum protein.

METHODS

The amino acids [11] used were prepared in concentrations of 5, 15 or 20 per cent in rubber-stoppered glass bottles, from which they were transferred to infusion flasks for intravenous administration, as needed. The maximal rate at which infusions were allowed to proceed was about 180 cc. per hour. The 15 and 20 per cent solutions were, however, always diluted to twice or three times their original volumes. Reactions following infusions did not occur. Occasionally, when infusion rates exceeded 200 cc. per hour, sensations of warmth and, rarely, of nausea were experienced. Reduction of the speed of flow usually relieved these symptoms promptly. The more cooperative patients became adept in regulating their own infusions. When large amounts of amino acids were given daily, it was found better to divide the dose into two or more parts, especially if the regular intake of food was not interrupted.

Determinations of nitrogen were carried out by the micro-Kjeldahl procedure. Serum albumin was estimated by the method of Campbell and Hanna.[12]

REPORT OF CASES

CASE 1.—C. A. A., a 19 year old man, a factory employee, was admitted to the hospital on Sept. 6, 1941 complaining of weakness and diarrhea. He had been well until November 1939, when he suffered an attack of severe diarrhea, which was diagnosed as ulcerative colitis; he was treated at home by his physician. A spontaneous remission of symptoms occurred. In July 1940 recurrence of severe colic, diarrhea, rectal bleeding and loss of weight caused his admission to the Third (New York University) Medical Division, Bellevue Hospital, where a second remission of symptoms took place after about two months. A month later he was transferred to Welfare Hospital for Chronic Diseases.

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9. Madden, S. C.; Zeldis, L. J.; Hengerer, A. D.; Miller, L. L.; Rowe, A. P.; Turner, A. P., and Whipple, G. H.: Casein Digests Parenterally Utilized to Form Blood Plasma Protein, J. Exper. Med. **73**:727, 1941.

10. (*a*) Farr, L. E., and MacFadyen, D. A.: Hypoaminoacidemia in Children with Nephrotic Crises, Am. J. Dis. Child. **59**:782 (April) 1940. (*b*) Cox, W. M., Jr., and Mueller, A. J.: Nitrogen Retention on Casein Digests, Proc. Soc. Exper. Biol. & Med. **42**:658, 1939. (*c*) Messinger, W. J.: Serum Protein Regeneration Following Use of Amino Acids in Nephritis (Nephrotic Stage), ibid. **47**:281, 1941. (*d*) Shohl, Butler, Blackfan and MacLachlan.[7]

11. The amino acids used in these studies were prepared by acid hydrolysis of casein, fortified with 1 per cent tryptophan. Eighty per cent of the total nitrogen is said to be present in the form of amino acid nitrogen. These amino acids were supplied by Frederick Stearns & Co.

12. Campbell, W. R., and Hanna, M. I.: Albumin, Globulins, and Fibrinogen of Serum and Plasma, J. Biol. Chem. **119**:15, 1937.

On examination, the patient appeared ill. There was marked loss of subcutaneous fat, the mucous membranes were pale and the skin had a sallow appearance. Diffuse abdominal tenderness and increase of peristalsis were present; otherwise there were no abnormalities.

The erythrocytes numbered 2,500,000 and the leukocytes 8,600 per cubic millimeter of blood. The hemoglobin amounted to 6 Gm. per hundred cubic centimeters. Study of blood smears revealed a moderate hypochromic, microcytic anemia and a normal leukocyte differential count. The Wassermann reaction was negative. The value for serum proteins was 5 Gm. per hundred cubic centimeters, of which 3 Gm. was albumin. Values for blood sugar, urea nitrogen, calcium and phosphorus were normal. No abnormalities were found on examination of the urine. Roentgenograms of the colon taken after a barium sulfate enema showed absence of haustrations and a smooth contour of the left half of the colon. Sigmoidoscopy revealed pale atrophic mucous membranes studded with many small scars. Numerous fresh bleeding points in the upper part of the rectum were also observed. Fresh

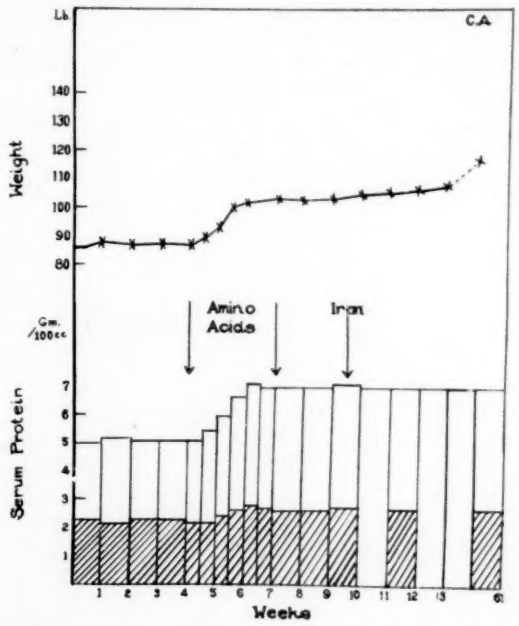

Chart 1 (case 1).—The weight curve and level of serum proteins are shown for periods before, during and after daily administration of 500 cc. of a 5 per cent solution of amino acids. The height of each column at the bottom of the chart represents the level of total serum proteins during the period shown; cross-hatched portion, serum globulin; the clear portion, serum albumin, except during the eleventh and thirteenth weeks, when only the total protein was measured.

stool removed through the sigmoidoscope contained some red blood cells and many epithelial cells but no pathogenic organisms or parasites.

The patient was placed at complete rest in bed. A bland diet rich in carbohydrate, containing 110 Gm. of protein daily and supplemented by parenteral vitamins was given. Small transfusions were administered frequently. Although he was afebrile and was passing only two formed stools containing but few red blood cells daily, he failed to gain weight and anemia persisted. A course of emetine hydrochloride was administered, without appreciable effect. On three occasions the patient suffered a recurrence of diarrhea (eight to ten loose stools daily) and cramps lasting a few days each. Two of these episodes were related to indiscretions in food, and the third followed a severe pharyngitis. During a period of three months, gain in weight and rise in the level of serum proteins or in the red blood

cell count failed to take place. It seemed reasonable, therefore, to use amino acid solutions as a means of supplying nitrogen.

Daily intravenous infusions of 500 cc. of a 5 per cent solution of amino acids, equivalent to 5 Gm. of nitrogen, and 5 per cent dextrose solution were given for twenty-one days as a supplement to his regular diet. They were generally given after breakfast and appeared to enhance the subject's appetite. At the end of the first week of this regimen a rise in the level of serum proteins and gain in weight began, and by the end of the third week the serum proteins had reached normal values (chart 1). Subjectively, improvement was marked by the fact that the patient became more hopeful of his eventual recovery. Little change in the red blood cell count or hemoglobin content occurred even after six weeks, and consequently 2 cc. of a solution of iron and ammonium citrates (0.5 Gm. of iron per cubic centimeter) was injected intramuscularly each day. During the next three weeks the red blood cell count and hemoglobin content rose to 3,900,000 and 11.8 Gm. respectively without, apparently, affecting the level of the serum proteins. Eight months after he had received the amino acids he continued well and the value of the serum proteins remained within the normal range, but a slight degree of anemia was still present.

TABLE 1.—*Nitrogen Balance and Level of Serum Proteins (in Case 2) Before and After Operation*

	Source of Nitrogen Intake per Twenty-Four Hours					Total Intake of Nitrogen per 24 Hr., Gm.	Total Output of Nitrogen per 24 Hr., Gm.	Nitrogen Balance	Serum Proteins, A/G Ratio
	Whole Blood		Amino Acids						
Day	Cc.	Nitrogen, Gm.	Cc.	Nitrogen, Gm.	Food Nitrogen, Gm.				
1	...	...	...	....	....	0	3.6	−3.6	3.0/2.8
2	...	...	...	....	....	0	3.0	−3.1	
3	...	...	...	....	....	0	3.4	−3.4	3.0/2.8
4	...	...	...	....	....	0	3.1	−3.1	
5	250	1.1	...	....	....	1.1	2.8	−1.7	3.0/2.8
6	250	1.1	150	3.0	....	4.1	3.7	+0.4	
7	250	1.1	250	5.0	....	6.1	5.8	+0.3	3.0/2.9
8	250	1.1	250	5.0	....	6.1	5.0	+1.1	
9*	500	2.1	500	10.0	....	12.1	1.7	+10.4	3.2/2.8
10	250	1.0	900	18.0	....	19.0	11.1†	+5.8	
							13.2		
11	250	1.0	900	18.0	....	19.0	10.8	+8.2	3.1/2.8
12	...	...	900	18.0	....	18.0	16.9	+1.1	3.0/2.8
13	...	...	900	18.0	....	18.0	13.4	+4.6	
14	...	...	750	15.0	....	15.0	11.6	+3.4	3.1/2.9
15	...	...	750	15.0	....	15.0	10.1	+4.9	3.3/3.0
16	...	...	600	12.0	....	12.0	9.6	+2.4	
17	...	...	600	12.0	2.0	14.0	9.4	+4.6	3.4/3.0
18	...	...	400	8.0	3.0	11.0	9.1	+1.9	
19	...	...	400	8.0	3.0	11.0	9.3	+1.7	
20	...	...	200‡	4.0	10.0	14.0	10.2	+3.8	3.4/3.0
21	...	...	100‡	2.0	11.0	13.0	10.0	+3.0	
22	...	...	...	...	16.0	16.0	10.7	+5.3	3.6/3.0

* Day of operation.
† In fifteen hours.
‡ Oral amino acids.

CASE 2.—R. H., a 32 year old white man, was admitted to the hospital on Nov. 16, 1940. He had apparently been well and working as a linesman until March 1938, when he first noticed discomfort in the upper part of the abdomen and eructations. A physician advised him that his symptoms were caused by a peptic ulcer. Several weeks later, chills, weakness and severe abdominal pain forced him to seek hospital care. He had at this time lost 30 pounds (13.6 Kg.). In September 1939 and again in March 1940 the same symptoms recurred accompanied by syncope, and on both of these occasions he was hospitalized. In May 1940, during the fourth admission to the hospital, a large mass was palpated by rectum in the cul-de-sac, and with the help of roentgen examination a diagnosis of regional ileitis was made. Surgical exploration was carried out, and a large mass in the cul-de-sac, made up of lymph nodes, cecum and terminal ileum adherent to the bladder and rectum, was found. Since the process was extensive, it was decided not to attempt removal. Roentgen irradiation of the abdomen was, however, followed by slight diminution in the size of the mass about the rectum. The patient was then transferred to this hospital.

On examination, marked emaciation was evident. The thighs were flexed on the abdomen to relieve abdominal pain. There was a long well healed rectus scar, and the lower portion of the abdomen was protuberant. The liver and spleen were not palpable, and the presence of abdominal fluid was not demonstrated. On rectal examination a moderately tender mass

about the size of a large grapefruit was palpated in the cul-de-sac. The rectum itself was not found to be abnormal by palpation or by proctoscopy. The results of physical examination were in other respects normal.

The erythrocytes numbered 3,400,000 and the leukocytes 7,700 per cubic millimeter of blood, and the hemoglobin content was 11.7 Gm. per hundred cubic centimeters. A differential count of the leukocytes showed that 80 per cent of them were polymorphonuclear leukocytes. The Wassermann reaction was negative. The serum proteins ranged between 5.5 and 5.8 Gm. per hundred cubic centimeters. The values for urea nitrogen, sugar, calcium and phosphorus of the blood were normal. The urine was normal throughout. Neither gross nor occult blood, pathogenic organisms or parasites were found in the stool. The reaction to a tuberculin test (old tuberculin in dilutions of 1 : 100,000 to 1 : 1,000) was negative. Repeated Frei tests gave negative reactions. Roentgenograms of the gastrointestinal tract taken after the ingestion of barium sulfate and of the rectum after a barium enema

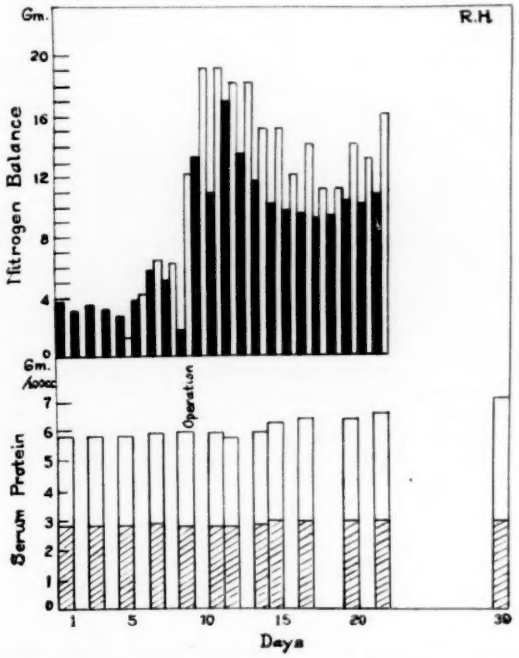

Chart 2 (case 2).—The nitrogen balance and the level of the serum proteins are shown for a nine day period prior to operation and for thirteen days after operation. Each solid black column represents nitrogen output for a twenty-four hour period, while the enclosed clear column, to the right of each black one, indicates the nitrogen intake for the same period. The nitrogen intake on the first four days was zero. The columns representing levels of serum protein are as described for chart 1.

revealed only distended loops of small bowel. On one occasion, the appearance of the roentgenogram suggested the diagnosis of tuberculosis of the cecum.

The patient was placed on a high calory diet rich in protein, carbohydrate and vitamin B complex. Bouts of nausea and vomiting and diffuse abdominal pain accompanied by visible hyperperistaltic waves continued to occur. Temporary relief was usually obtained by the use of atropine, narcotics or Wangensteen drainage. During a period of four months, improvement failed to occur. Since hypoproteinemia persisted, two infusions of 150 cc. each of a 15 per cent solution of amino acids (6 Gm. of nitrogen) diluted to 450 cc. with 5 per cent dextrose solution were given daily for fourteen days, without increase in the serum proteins or improvement in the nutritional state. Because the presence of symptoms and

signs of partial obstruction made surgical intervention appear inescapable, an attempt was made to maintain the patient in nitrogen equilibrium and furnish his caloric requirements entirely by intravenous infusion in order to afford rest to the gastrointestinal tract before operation. For four days preceding operation food was not given by mouth. The only food available was given intravenously in solutions containing 15 per cent amino acids and 10 per cent dextrose and in a few small transfusions of whole blood (table 1). The number of calories furnished by this material generally exceeded 1,500 for each twenty-four hour period. Minerals were supplied by adding concentrated Ringer-Locke solution to the infusions. The patient volunteered the information that his abdominal pain decreased markedly during this period.

At operation, a large pelvic mass was found in the cul-de-sac. It consisted of loops of ileum, cecum and a considerable amount of acute and chronic inflammatory tissue. The tip of the appendix was, on careful dissection, found to be incorporated in the mass. Gross and microscopic study of the specimen removed at operation failed to decide whether the original condition was a regional ileitis involving the cecum and appendix or an appendical abscess involving the ileum.

For eight days after operation, the patient was, except for small transfusions (table 1), fed parenterally with solutions of dextrose and amino acids. His nutritional state was excellent, judged by prompt healing of his wound, continuous positive nitrogen balance and increase in serum proteins (chart 2). The nitrogen derived from transfusions was calculated from the serum protein content and amount of blood used. Five months after operation, the patient was fairly well. His weight was 141 pounds (64 Kg.), and he was earning his livelihood. Serum proteins were within normal limits and at about the level shown on the thirty-ninth day after operation (chart 2).

CASE 3.—C. H., a 21 year old white woman, was admitted to the hospital on April 31, 1940, with complaints of generalized edema, headaches and irregularity of the menses. Of interest in her past history were the facts that she had suffered an uncomplicated attack of scarlet fever in childhood and that she had had otitis media necessitating myringotomy at the age of 17.

During the summer of 1937, while traveling in Europe, the patient became ill of a severe infection of the upper respiratory tract, which subsided in about ten days. On her return to this country four months later, puffiness about the eyes and edema of the ankles were noted, and she was told by her physician that she had nephritis. A year later generalized edema appeared. During the three year interval between the onset of the edema and admission to this hospital, the patient felt quite well, although it was learned from the physician's record that large amounts of albumin and numerous formed elements were regularly found in the urine and that hypoproteinemia, hypercholesteremia and anemia were continually present. Arterial pressure was normal.

On examination, the generalized edema and puffiness about the eyes were seen to be marked. The skin was pasty. Slight increase in light reflex of the retinal arteries was noted. The arterial pressure varied between 140 and 160 mm. of mercury systolic and 96 and 110 mm. diastolic. Examination otherwise showed nothing abnormal.

There were 2,750,000 red blood cells per cubic millimeter and 9 Gm. of hemoglobin per hundred cubic centimeters of blood. The leukocytes were normal as to number and variety. The level of sugar in the blood was 86 mg. per hundred cubic centimeters, urea nitrogen 28 to 33 mg., total cholesterol 830 to 1,100 mg., total protein 3.94 to 4.8 Gm. (albumin about 1.5 Gm. and globulin 2.5 Gm.), calcium 8.6 mg., phosphorus 5.9 mg. and phosphatase 9.2 Bodansky units. The Wassermann reaction of the blood was negative. The basal metabolic rate was —15 per cent. Roentgenograms showed the heart to be enlarged to the left and demonstrated coarse trabeculations of the humeri. The electrocardiogram was normal. Examination of the urine yielded a maximal specific gravity of 1.012. Seven to 10 Gm. of albumin was found regularly in each twenty-four hour specimen of urine. The centrifuged sediment under the microscope showed 1 or 2 granular casts per high power field, occasional waxy casts, white blood cells and rare red blood cells. Doubly refractive bodies were shown to be present by the polarizing microscope. Phenolsulfonphthalein excretion was 27.5 per cent in two hours. The standard urea clearance was 38.2 per cent of normal.

The patient was placed on a salt-poor, low fat diet containing 120 Gm. of protein and on 1,500 cc. of fluid daily. After an observation period of one month, 500 cc. of a 5 per cent solution of amino acids with 5 per cent dextrose was administered daily for fourteen days in addition to the regular diet. Total output of urinary nitrogen, including the albumin

nitrogen, was determined daily for seven day periods before, during and after the fourteen day period of treatment. Values for fecal nitrogen and serum protein were obtained frequently. Increase in the level of the serum proteins failed to occur (chart 3), and there was no change in the output of urinary albumin. During the period of study, consumption of the diet was complete. The weight was constant; the hematocrit value did not change, and there was no obvious change in the clinical condition.

The patient was readmitted to the hospital in October 1940, seriously ill with diffuse bilateral bronchopneumonia, shown by physical examination and roentgenograms of the lungs. During the period of acute infection, the total cholesterol level in the blood decreased and the serum proteins increased (chart 4). When she recovered, both values returned to previous levels. The blood pressure on admission was 136 to 160 mm. of mercury systolic and 100 diastolic. Renal function as shown by phenolsulfonphthalein excretion and urea clearance had not changed appreciably. In April 1941 the patient was again readmitted for study. The albumin portion of the serum proteins was for the first time noted to be greater than the globulin (chart 4). Since this time, frequent observation in the clinic shows that the blood pressure has been increasing (systolic level at the time of writing 156 to 164 and diastolic 110 mm. of mercury), while edema and body weight have been decreasing. The degree of anemia is unchanged. The urea nitrogen content of the blood has risen to 54 mg. per hundred cubic centimeters and the level of the serum proteins to 6 Gm., with albumin 3.3 Gm. and globulin 2.7 Gm. The total cholesterol content of the blood has decreased to 384 mg. per hundred cubic centimeters. Renal function as measured by the standard urea clearance has fallen steadily to 25 per cent of normal, and phenolsulfonphthalein excretion has diminished to 21 per cent in two hours (chart 4). Doubly refractive bodies are no longer demonstrable in the urine. The albumin content of twenty-four hour specimens of urine now ranges from 3 to 5 Gm. per hundred cubic centimeters.

CASE 4.—J. C., a 41 year old white man, was admitted to the hospital on April 4, 1940, with the chief complaint of swelling of the legs; he left the hospital against advice two months later and was readmitted on August 4, during which admission the present study was begun. He suffered an attack of scarlet fever in childhood and had gonorrhea at the age of 17 and had been subject to heroin (diacetylmorphine) addiction since the age of 21. The present illness began in 1938, with edema of the ankles, gradually progressing to anasarca within two months. On his admission to a hospital at that time, it was noted that the urine showed a 4 plus reaction for albumin and contained occasional red blood cells and casts and that the concentration of serum proteins was low (3.5 Gm. per hundred cubic centimeters), with albumin and globulin present in equal quantities.

On examination, a poor state of nutrition and pallor were obvious. The systolic blood pressure varied from 130 to 160 and the diastolic from 94 to 104 mm. of mercury. Slight increase of the light reflex of the retinal arteries was present. Numerous pigmented pitted scars of the skin of the extremities, trunk and abdomen were said by the patient to be the sites of injections of the narcotic during the last fifteen years or more. Examination otherwise showed nothing abnormal.

The red blood cells numbered 2,800,000 and the leukocytes 7,300 per cubic millimeter, and 11 Gm. of hemoglobin was present in each hundred cubic centimeters of blood. The values for sugar, calcium and phosphorus in the blood were normal. The blood urea nitrogen varied from 26 to 42 mg. per hundred cubic centimeters, the serum proteins from 4 to 4.8 Gm., the albumin fraction from 2.4 to 2.8 Gm. and the total serum cholesterol from 450 to 600 mg. The Congo red absorption test was not indicative of amyloid disease. The Wassermann reaction of the blood and the spinal fluid was negative. Examination of the urine showed a maximal specific gravity of 1.014, an albumin content of 6 to 12 Gm. in twenty-four hours and absence of reducing agents. Microscopic examination of centrifuged sediment regularly showed occasional granular and hyaline casts, a few white blood cells and rare red blood cells. Doubly refractive bodies in the urine were frequently demonstrable. The standard urea clearance was 28 per cent of normal, and the phenolsulfonphthalein excretion was 20 per cent in two hours.

The patient was placed on a salt-poor, low fat diet, containing 120 Gm. of protein. His fluid intake was regulated at 1,500 cc. in twenty-four hours. From 15 to 30 mg. of morphine sulfate was necessary five times daily to control the symptoms of addiction, and all efforts to stop use of the drug failed. Generally, he consumed the major portion of his diet but occasionally complained of anorexia and lassitude. Additional amounts of protein and iron given orally did not affect the hypoproteinemia or anemia. After a preliminary period of observation (one month) daily intravenous injections of 180 cc. of 20 per cent solution of amino acids [11] diluted with an equal quantity of distilled water were

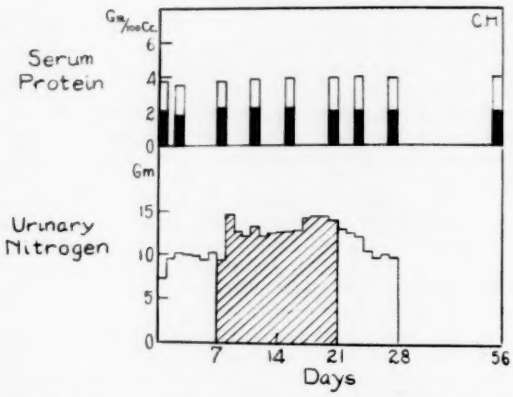

Chart 3 (case 3).—The level of the serum proteins and the urinary nitrogen excretion are shown for periods before, during and after the intravenous administration of amino acids. The light portion of the columns which represent total serum proteins indicates the level of serum albumin. The urinary nitrogen excreted during each twenty-four hour period is shown in blocks at the bottom of the chart. The cross-hatched area indicates the period during which 500 cc. of a 5 per cent solution of amino acids was injected daily. Significant change in the level of serum proteins did not occur.

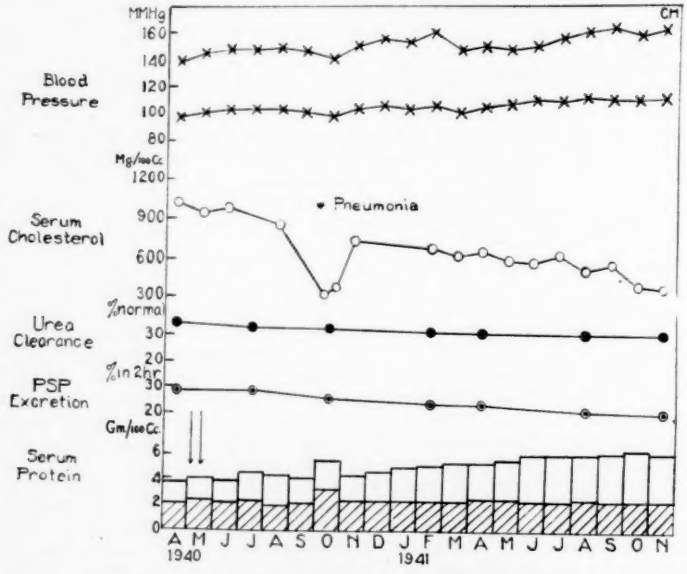

Chart 4 (case 3).—Pertinent data obtained during a twenty month period of observation. Progressive increase in blood pressure is accompanied by decrease in lipemia and renal function. The arrows indicate the period of intravenous amino acid therapy (detail shown in chart 3). Of interest are the abrupt decrease in the cholesterol values and the increase of the globulin fraction of the serum protein during the period of acute febrile illness.

given for eighteen days in addition to the regular diet. Each 100 cc. of undiluted amino acids contained 2 Gm. of nitrogen. The total output of urinary nitrogen, including albumin, was measured for periods of one week before, during and after the period of administration of the amino acids. Values for fecal nitrogen and serum protein were obtained frequently. After the series of injections of amino acid solutions was completed, a small but definite rise in proteins was noted and the level continued to rise, reaching a peak thirty-six days later (chart 5). The increase in the serum protein level occurred chiefly in the albumin fraction. During the next three months, the serum proteins fell slowly to the previous level and the patient became listless, eating his diet only on constant persuasion.

The patient was then restudied under the same conditions except that larger amounts of amino acids were administered. Three hundred cubic centimeters of 15 per cent (2 Gm. of nitrogen per hundred cubic centimeters) solution diluted with an equal amount of water was given daily for sixteen days. During the first week of administration, a perceptible rise in serum proteins was noted (chart 5) and the increase continued to a peak of 5.9 Gm. per hundred cubic centimeters twelve days after cessation of therapy. The increase again occurred in the albumin fraction. During both periods of therapy there was fairly complete consumption of diet; body weight and hematocrit values were constant. During the latter part of the second period of therapy the patient stated that he thought he could

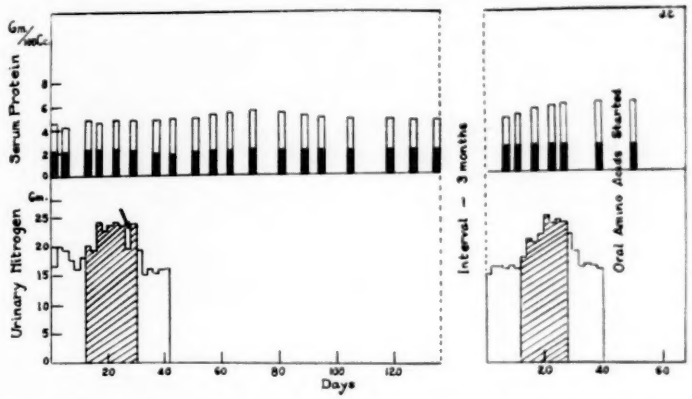

Chart 5 (case 4).—The level of the serum protein and the urinary nitrogen output are shown for periods before, during and after the intravenous administration of amino acids. The light portion of the columns which represent total serum proteins indicates the level of serum albumin; the solid black, serum globulin. The urinary nitrogen excreted during each twenty-four hour period is shown in blocks at the bottom of the chart. The cross-hatched areas indicate the periods during which 180 cc. of a 20 per cent solution and 300 cc. of a 15 per cent solution of amino acids respectively were given daily. During a two day period the administration of amino acids was omitted; the arrow points to the drop in urinary nitrogen.

diminish his daily morphine requirements, and at the end of the period he voluntarily ceased its use. As far as can be judged, he has not reverted to its use again. He was discharged from the hospital on June 15, 1941 and has been periodically observed in the clinic.

Since the patient's condition appeared excellent, it was decided to test whether serum protein levels might be maintained by the oral administration of the same preparation of amino acids used intravenously. He has therefore ingested 300 cc. of a 15 per cent solution in addition to his regular diet every two days ever since, without difficulty. Five months after discharge his serum proteins were still at a level of 5.8 to 6 Gm. per hundred cubic centimeters. Arterial pressure, serum cholesterol, phenolsulfonphthalein excretion and urea clearance values changed but little (chart 6). The urine still showed a maximal specific gravity of 1.014, with the albumin content and the variety of formed elements in the sediment unchanged. The patient seems to be in fair health and has no complaints except constant slight edema of the ankles. The anemia has persisted. For the first time in three years, he is gainfully employed.

CASE 5.—L. L., a 60 year old Norwegian, a former seaman, was admitted to the neurologic service on Aug. 6, 1939 because of difficulty in walking for the past fifteen years and increasing dysarthria for nine years. The only seemingly relevant facts in the history were that he had gonorrhea and a chancre in his youth.

On examination, the patient appeared poorly nourished and pale. The retinal arteries exhibited arteriosclerotic changes. The tongue deviated to the right on protrusion. The heart and lungs were essentially normal on both physical and roentgen examination. The arterial pressure was 100 systolic and 60 diastolic. The abdomen was normal, but muscular tone was poor. The peripheral arteries were beaded and tortuous wherever palpable. Neurologic signs pointed to diffuse involvement of pyramidal and cerebellar tracts and to moderately advanced mental deterioration. The extremities showed atrophy of the muscles. Edema was not present.

The number of erythrocytes varied from 3,800,000 to 4,000,000 per cubic millimeter. Each 100 cc. of blood contained 11 to 12 Gm. of hemoglobin. The leukocytes numbered 8,200 per cubic millimeter, of which 70 per cent were polymorphonuclear leukocytes and 30 per cent lymphocytes. The urine was normal. The Wassermann reaction of both blood

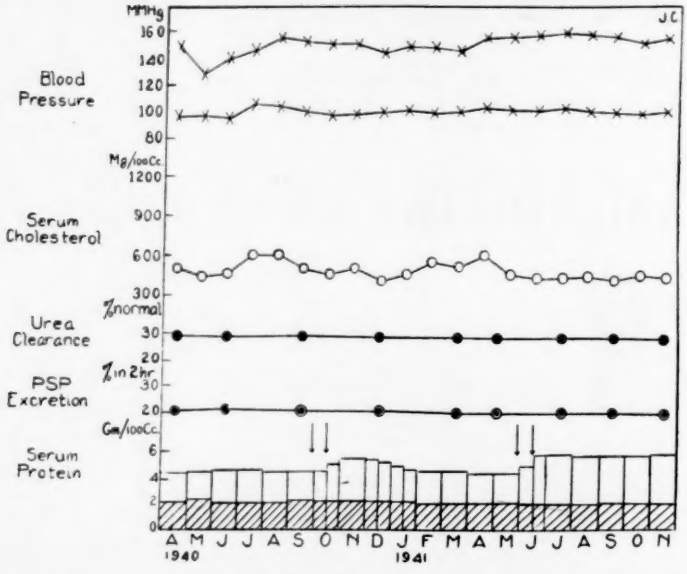

Chart 6 (case 4).—Pertinent data obtained over a twenty month period of observation. Few changes are noted except in the values for serum protein. The height of each column at the bottom of the chart represents the average of three or more measurements of total serum proteins obtained during each month; the cross-hatched areas, serum globulin, and the clear portion, serum albumin. Two sets of arrows indicate the intervals during which amino acids were given intravenously (details shown in chart 5). Increases in serum protein follow both periods of therapy and have been maintained after the second period by the oral administration of amino acids.

and spinal fluid was negative, and the colloidal gold curve of the spinal fluid was normal. Total serum proteins never exceeded 4.8 Gm. per hundred cubic centimeters while the subject was under observation. The albumin content of the serum was regularly 3 Gm. per hundred cubic centimeters. Values for blood sugar and urea nitrogen, total cholesterol and cholesterol esters were always within normal limits.

The patient's difficulties were ascribed chiefly to cerebral arteriosclerosis. Occasional febrile episodes probably due to ill defined areas of bronchopneumonia occurred. Frequent periods of complete anorexia, sometimes necessitating gavage, and lack of sufficient protein intake were thought to be factors contributing to the hypoproteinemia. On three separate occasions, during periods of complete anorexia, infusions of 500 cc. of 5 per cent amino

acids with 5 per cent dextrose solution were followed by immediate return of appetite and request for food. Infusions of 5 per cent dextrose solution alone did not secure this response. He was then given 500 cc. of 5 per cent solutions of amino acids (5 Gm. of nitrogen) with 5 per cent dextrose daily, intravenously, in addition to his regular diet, containing 100 Gm. of protein, in an effort to raise the level of the serum protein. Two weeks of daily infusions of amino acids failed to raise the level of the serum proteins.

The patient died of an intercurrent pneumonic infection four months after the period of observation. Postmortem examination of the brain substantiated the diagnosis of cerebral arteriosclerosis with involvement of pyramidal and cerebellar structures. The lungs exhibited numerous small areas of consolidation. The state of the liver was, of course, of especial interest, since one obvious reason for failure to regenerate serum proteins is impairment of that function of the liver which is responsible for their elaboration. It weighed 600 Gm. and appeared brownish red, and its surface was finely granular. On section, lobulation appeared prominent, and the parenchyma had a peculiar dull brown appearance. Microscopically, the lobules of the liver were surrounded by fine strands of connective tissue and scattered lymphocytes. The hepatic cells were small and in some instances vacuolated. Vacuolation was shown by the use of special stains to be due neither to fat nor to glycogen. The significance of these observations will be discussed.

COMMENT

The observation in 1 case (case 2) that solutions of amino acids administered intravenously can maintain nitrogen equilibrium (chart 2) when these substances are the only source of nitrogen available confirms previous reports by other workers.[13] It is probable that when quantities as large as 900 cc. of a 15 per cent solution are administered daily (case 2) appreciable amounts may be lost in the urine, but the continuous positive nitrogen balance achieved postoperatively in case 2 makes it evident that a large proportion of the acids was utilized. Particular attention is directed to the large output of nitrogen in this case in the days immediately following operation. Although Elman [13a] has recently emphasized the fact that the occurrence of this phenomenon is a frequent postoperative event, its importance with regard to replacement therapy has not been generally appreciated.

Increase in serum proteins following the intravenous use of amino acids has been more difficult to demonstrate than simple maintenance of nitrogen equilibrium. It is believed that such increases have been shown to occur in 3 patients in the present study (cases, 1, 2 and 4). The fact that these patients were observed for over considerable periods prior to the administration of amino acids without exhibiting increases in serum protein under very favorable circumstances of environment and diet makes it extremely unlikely that the increases in serum proteins observed after administration of amino acids were unrelated to this event. Since the reasons for the existence of the hypoproteinemia in the patients under discussion were, in all probability, different, the results obtained will be described in detail.

The increase in serum protein followed closely by increase in body weight (case 1) suggests that the amino acids not only contributed to the regeneration of serum protein but may have contributed to rebuilding of other protein tissues of the body. It is interesting also that the increase in total serum protein took place in the albumin fraction, just as is the case in periods of spontaneous improvement in instances of cirrhosis of the liver. Despite a return of the serum proteins to normal levels, anemia persisted. Since iron taken orally tended to cause diarrhea in this patient, large amounts of parenteral iron were given; the anemia responded slowly to this therapy, but, contrary to expectations, the new hemoglobin was formed without a fall in the serum proteins. Persistence of hypoproteinemia

13. (*a*) Elman, R.: Parenteral Replacement of Protein with the Amino-Acids of Hydrolyzed Casein, Ann. Surg. **112**:594, 1940. (*b*) Shohl, Butler, Blackfan and MacLachlan.[7]

and anemia in spite of the fact that the patient's diet was considered adequate in all essentials necessary for regeneration of serum protein and production of hemoglobin may be explained by deficient absorption from a defective gastrointestinal tract. Whether or not a defect was present, it is clear that the administration of easily utilizable intravenous acids helped this patient retain sufficient nitrogen for regeneration of serum protein, repletion of protein stores and production of hemoglobin.

That in case 2 the serum proteins prior to operation failed to increase was not unexpected, since it is well known that in the presence of infection the mechanism of serum protein regeneration may be impaired. When the source of infection was surgically eradicated, however, a small increase in serum proteins began to be apparent on the sixth day after operation, and the level continued to rise slowly. This fact is of especial significance because the only source of nitrogen available during the postoperative period was supplied in the form of parenterally

TABLE 2.—*Data on a Group of Patients Treated with Amino Acids Intravenously*

Patient	Age	Sex	Diagnosis	Complicating Factor	Response to Intravenous Amino Acids
H. R.	54	F	Hypertensive cardiovascular disease; right hemiplegia; parkinsonism; diabetes mellitus	Stone in common duct, with jaundice; diabetic acidosis	Appetite and diabetic control restored
I. B.	27	F	Rheumatoid arthritis of hips and spine	Bilateral arthroplasty of hip	Severe anorexia following each operation, corrected in each instance
M. B.	31	F	Postencephalitic parkinsonism	Hyoscine toxicity	Anorexia uncontrolled by usual therapy, including intravenous injection of electrolytes; return of appetite five hours after use of amino acids
R. L.	22	F	Hodgkin's disease	Nausea, vomiting and anorexia following roentgen therapy	Prompt cessation of symptoms on two occasions
M. L.	68	M	Hypertrophy of prostate with diminution of renal function	Intestinal obstruction caused by carcinoma of sigmoid; resection of left portion of colon	Complete anorexia for no apparent reason ten days after operation; patient objected violently to gavage; anorexia overcome

administered amino acids. Rapid healing of the wound and an otherwise unusually smooth convalescence confirm previous observations concerning the importance of maintaining nitrogen balance and normal serum protein values in surgical patients.[14]

The increase in serum proteins following injections of amino acids in case 4 and the failure to increase in case 3 were discussed in a previous communication.[10c] The results are now reviewed after long periods of observation. At the time of the first report the 2 patients appeared to exhibit similar clinical and laboratory data, but it may be significant that in 1 (case 3) the condition has progressed into a rather typical chronic nephritis while similar changes have not taken place in the other (case 4), who appears at the time of writing to be in a fair state of health. In case 4, as in case 1, the increase in the albumin fraction was responsible for the rise in the level of serum protein. The ability of orally ingested amino acids to maintain the increase in the serum protein obtained by the intra-

14. (*a*) Whipple, A. O.: The Critical Latent or Lag Period in the Healing of Wounds, Ann. Surg. **112**:481, 1940. (*b*) Mecray, P. M.; Barden, R. P., and Ravdin, I. S.: Nutritional Edema: Its Effect on the Gastric Emptying Time Before and After Gastric Operations, Surgery **1**:53, 1937. (*c*) Jones and Eaton.[1a]

venous use of amino acids has now been satisfactorily demonstrated over a period of nine months. The fact that the patient (case 4) failed to regenerate serum protein or hemoglobin on a diet that was considered adequate for these purposes until he was given amino acids intravenously raises an interesting problem. Whether his ability to absorb proteins as such from the gastrointestinal tract is impaired or whether he lacks certain of the enzyme systems necessary for the breakdown and subsequent utilization of proteins after they have been absorbed is not apparent from this study. That he was able subsequently to maintain the serum protein level with orally ingested amino acids suggests that his difficulty lies in handling of whole proteins and their split products. It is so unusual as to be worthy of note that twenty years' addiction to a narcotic (heroin [diacetyl morphine]) has been interrupted.

In a recent review on the plasma proteins, Madden and Whipple [15] discussed the role of the liver in the formation of these substances, and the evidence presented points to that organ as being the site of production of albumin, fibrinogen and at least part of the globulins in the experimental animal. If the liver is the organ largely responsible for the formation of the plasma proteins in man as well, then the finding at autopsy of an atrophic liver in 1 of our patients (case 5) is a possible explanation for his inability to manufacture new serum proteins. In this connection the report of a dog with an Eck fistula that could form only about one tenth as much plasma protein on a standard diet as could control animals may be mentioned.[16] This animal consequently remained hypoproteinemic. At autopsy, the liver was found to be markedly atrophic.

The return of appetite following intravenous administration of amino acids (case 5) has been repeatedly demonstrated in our hospital in a variety of clinical states, but attempts were not made to study the utilization of the injected material. Table 2 briefly summarizes the data on a group of 5 patients, who were thus treated after the usual methods failed to relieve the apathy for food.

CONCLUSIONS

Amino acid solutions [11] intravenously administered in sufficient quantities have been shown in 1 instance to maintain positive nitrogen balance.

In certain patients injections of intravenous amino acids are followed by increases in serum proteins.

Solutions of amino acids given intravenously appear to be of value in relieving intractable anorexia.

15. Madden, S. C., and Whipple, G. H.: Plasma Proteins: Their Source, Production and Utilization, Physiol. Rev. **20**:194, 1940.

16. Knutti, R. E.; Erickson, C. C.; Madden, S. C.; Rekers, P. E., and Whipple, G. H.: Liver Function and Blood Plasma Protein Formation, J. Exper. Med. **65**:431, 1937.

TRICUSPID STENOSIS

INCIDENCE AND DIAGNOSIS

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Data concerning the incidence of tricuspid stenosis recently have been compiled by Cooke and White.[1] This indicates that the tradition of the rarity of tricuspid stenosis may be partly due to numerous compilations of isolated case reports and to discrepancies dependent on variations in defining stenosis. These investigators found that between 1920 and 1937 there were 217 cases of rheumatic heart disease noted in 4,300 autopsies at the Massachusetts General Hospital. In 47 of these the tricuspid valve was affected, and in 30 there was tricuspid stenosis thought to be of sufficient degree to be of clinical significance.

In these 30 cases of Cooke and White [1] the diagnosis was made before death in 1 and suspected in 2 more. Their conclusion was that the diagnosis of tricuspid disease is difficult, but that if due attention were paid to the history and the clinical examination of the patient and to the roentgenogram of the heart, the diagnosis would be made more frequently. No one sign in their experience was pathognomonic, but they listed in order of importance the following clues: a middiastolic murmur localized over the tricuspid area, chronic and well marked systolic pulsation of the deep jugular veins, ascites in the absence of congestion of the lungs, enlargement of the shadow of the heart to the right, deviation of the esophagus to the left, cyanosis and sometimes jaundice, enlargement of the liver with or without pulsation, persistently raised venous pressure and a prolonged circulation time for the right side of the heart.

This study of tricuspid stenosis is based on 13 cases proved to be such post mortem at the Cleveland City Hospital in the decade from January 1930 to December 1939, inclusive. During this period there were 6,548 autopsies, of which 119 pertained to patients who died primarily of rheumatic heart disease (there were many others that showed slight involvement of the heart by rheumatic fever). The 119 patients with fatal rheumatic heart disease included 43 (36.1 per cent) who had involvement of the tricuspid valve, in 13 of whom the process had advanced to definite tricuspid stenosis (10.9 per cent of the 119).

The valves affected in the whole group of 119 patients were:

Mitral alone	28
Aortic alone	3
Mitral and aortic	45
Mitral and tricuspid	4
Mitral, aortic, and tricuspid	34
Mitral, tricuspid and pulmonic	1
Mitral, aortic, tricuspid, and pulmonic	4
	119

From the Department of Medicine of the Cleveland City Hospital and the Western Reserve University School of Medicine.

1. Cooke, W. T., and White, P. D.: Tricuspid Stenosis, with Particular Reference to Diagnosis and Prognosis, Brit. Heart J. **3**:147 (July) 1941.

Thus, of 119 cases of death from rheumatic heart disease, the mitral valve was affected in 116 cases, the aortic in 86, the tricuspid in 43 and the pulmonic in 5.

Study of the 13 cases of tricuspid stenosis failed to reveal any symptoms or signs valuable in diagnosis beyond those listed by Cooke and White. It was possible, however, to support especially a point brought out by Cooke and White in reference to pulsation in the neck veins. These investigators found that deep jugular pulsation signified tricuspid regurgitation only, whether due to functional or to organic disease. But they felt that there was a *"strong probability, in fact almost a certainty, of the presence of tricuspid stenosis in the case of a patient in the fourth or fifth decade with rheumatic heart disease who has had for years marked systolic deep jugular pulsation with little or no congestive failure."*

In the series studied here, of the 119 persons who died of rheumatic heart disease, 7 had significant chronic organic tricuspid insufficiency. Of these, at autopsy, 6 showed marked tricuspid stenosis; the seventh, slight stenosis. In short, *there was not a single case of organic tricuspid insufficiency without stenosis of some degree.* It would appear that the presence of tricuspid insufficiency considered clinically to be organic is strong evidence in favor of the diagnosis of tricuspid stenosis.

Of the 13 cases of tricuspid stenosis, 3 were diagnosed clinically. One of these is reported, chiefly because the stenosis was extraordinarily severe.

REPORT OF A CASE

J. D., a white man aged 36, who entered the Cleveland City Hospital Oct. 21, 1938, complained of shortness of breath. He had been in good health until May 1937, when he noticed weakness, shortness of breath on exertion, cough and swelling of his ankles. These symptoms became increasingly severe, so that he was virtually incapacitated during the year before he was admitted to the hospital. An acute psychosis with an attempt at suicide was the immediate cause for hospitalization. There was no past history of rheumatic fever.

Examination showed the patient to be well developed but orthopneic and acutely ill. The skin and the mucous membranes showed a combination of moderate cyanosis and slight icterus. The veins of the neck were distended with blood and pulsated. There were rales at the bases of the lungs. The liver was enlarged, the edge being 6 cm. below the costal margin, and definitely seemed to pulsate. The legs and the back were edematous.

The heart was much enlarged in all directions. There was a systolic thrill at the base, with a diastolic one at the apex. At the base and to the left of the upper part of the sternum there were a systolic and a diastolic murmur, the latter having the characteristics of one due to aortic insufficiency. At the apex there was a systolic murmur, as well as a diastolic murmur of a rumbling nature with a presystolic accentuation. In addition, a systolic and a diastolic murmur were noted in the xiphoid region. The cardiac mechanism was normal, and there was a gallop rhythm. The pulse was of the Corrigan type. The blood pressure was 184 systolic and 60 diastolic.

The venous pressure was 22 cm. of blood, and this increased to 28 cm. when the liver was pressed on. The decholin circulation (arm to tongue) time was forty-one seconds, and the ether circulation time was thirteen seconds. The vital capacity was 3,000 cc., which was 68 per cent of the estimated normal. Wassermann tests of the blood and the spinal fluid gave normal results. The specific gravity of the urine was 1.032; the reaction for albumin was grade 4. The red blood cell count was 6,000,000 per cubic millimeter, and the value for hemoglobin was 22.3 Gm. per hundred cubic centimeters of blood.

Fluoroscopic examination of the heart and roentgenograms of the chest showed the cardiac shadow to be considerably increased in size in all directions. The transverse diameter measured 23 cm. in relation to the greatest internal diameter of the chest, which was 35 cm. The left ventricle was greatly increased in size in both the posteroanterior and the second oblique view. In the first oblique view the left auricle was slightly enlarged and the pulmonary conus was prominent. The pulsations of the heart were increased in amplitude and were regular. The aorta was normal. The lung fields were clear.

The electrocardiogram showed left axis deviation, low voltage and splintering of the QRS complex in lead III.

Despite appropriate treatment the patient's cardiac failure became increasingly severe. He died Jan. 7, 1939.

The clinical diagnosis was rheumatic heart disease with aortic insufficiency and stenosis, mitral stenosis and insufficiency, tricuspid stenosis and insufficiency, cardiac hypertrophy and dilatation, and myocardial insufficiency.

Autopsy (Dr. L. L. Terry).—External findings were negative except for pitting edema of the legs.

The heart weighed 825 Gm. The right atrium was slightly dilated, and the musculature was hypertrophied. The orifice of the tricuspid valve had a fish mouth appearance, the circumference measuring 3.5 cm. (figure). The right ventricle was relatively small, and the wall measured 4 mm. in thickness. The pulmonary valve was normal.

The left atrium was moderately dilated; the wall was thickened and the endocardium more opaque than usual. The mitral valve showed a moderate degree of stenosis, the circumference of the orifice being 6 cm. The left ventricle was markedly enlarged, and the wall measured 19 mm. in thickness. The cusps of the aortic valve were adherent, and the edges were thickened and rolled in toward the sinuses of Valsalva. The coronary arteries were normal.

A markedly stenosed (fish mouth) tricuspid valve seen from above, in a case of chronic rheumatic heart disease.

The lungs showed severe chronic passive hyperemia with numerous recent and remote infarcts. The liver weighed 2,100 Gm. and was the site of typical cardiac cirrhosis. The remaining viscera showed chronic passive hyperemia.

The diagnosis was chronic rheumatic heart disease with hypertrophy and dilatation; chronic rheumatic endocarditis with stenosis and insufficiency of the mitral, aortic and tricuspid valves; infarcts of the lungs; thrombi in the pulmonary arteries; cardiac cirrhosis of the liver, and chronic passive hyperemia of the viscera.

COMMENT

The clinical diagnosis of tricuspid insufficiency and stenosis in this case was made principally on the basis of the combination of a systolic and a diastolic murmur in the xiphoid region, the systolic jugular pulsation, the pulsation of the liver and the peculiar cyanotic-icteric appearance of the patient.

The degree of stenosis of the tricuspid valve was very severe. In none of the other cases studied was the stenosis as severe. It is notable that with an orifice so stenosed the jugular veins and the liver nevertheless showed pulsations. This indi-

cates that stenosis of even extreme degree need not prevent the phenomenon of insufficiency of the valve. The importance of the organic tricuspid insufficiency as an indication of probable stenosis has been noted.

Such marked tricuspid stenosis occurring in a male is also noteworthy. Smith and Levine,[2] for example, have pointed out the preponderance of females with tricuspid stenosis, and have written that in their personal experience they have never encountered a male with marked tricuspid stenosis.

Smith and Levine also stated that in their cases the degree of stenosis of the mitral valve was always as great as or greater than that of the tricuspid valve. Again this case is exceptional, for the tricuspid stenosis was more severe than the mitral stenosis.

SUMMARY

Of 119 consecutive patients who died of rheumatic heart disease and were examined post mortem, 43 (36.1 per cent) showed involvement of the tricuspid valve, and in 13 of these the process had advanced to definite tricuspid stenosis (10.9 per cent of the 119 cases of rheumatic heart disease).

No new symptoms or signs helpful in diagnosis were discovered. The study did emphasize, however, the importance of chronic organic rheumatic tricuspid insufficiency as an indication that stenosis is likely, for in all the 7 cases of organic tricuspid insufficiency included in the series there was more or less stenosis.

Three cases of tricuspid stenosis were diagnosed clinically. One of the patients had very severe tricuspid stenosis, the circumference of the orifice measuring 3.5 cm. Nevertheless, clinically there was pulsation of the jugular veins and of the liver. Apparently marked stenosis of the tricuspid valve need not prevent the phenomena of tricuspid insufficiency.

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2. Smith, J. A., and Levine, S. A.: The Clinical Features of Tricuspid Stenosis, Am. Heart J. **23**:739 (June) 1942.

CHOLESTEROL CONTENT OF THE URINE IN PATIENTS WITH CANCER

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In recent years, there has been an unusual amount of conjecture as to the significance of the configurational similarity of the sex hormones, bile acids, vitamin D, cholesterol and the carcinogenic polycyclic hydrocarbons. Much speculation has been devoted particularly to the chemical relationship between the sex hormones and carcinogenic principles in the etiology of cancer. Sobotka [1] quoted Cook, who stated that "the cell proliferation which characterizes the estrous state is in some respects reminiscent of the early stages of malignant growth," and Sobotka further conjectured that, while biodehydrogenation of sterols or bile acids may be the physiologic method for the production of the sex hormones, further dehydrogenation by a faulty mechanism may give rise to tumor-stimulating substances.

Sobotka and Bloch [2] were unable to find any positive chemical or biologic evidence for the presence of carcinogenic hydrocarbons in large quantities of pooled urine from patients with cancer. However, they were able to confirm their previously reported observation [3] that urine from such patients contained larger quantities of cholesterol than that of normal subjects. The hypercholesteruria was attributed either to an anomaly of cholesterol metabolism inherent in persons with cancer or to destruction of malignant tumor tissue, which is known to be rich in cholesterol. The latter theory was given preference. Cachexia as a possible cause for the increased excretion of urinary cholesterol was ruled out by control studies on cardiac and tuberculous patients. In 1940, Sobotka, Bloch and Rosenbloom [4] analyzed individual twenty-four hour specimens of urine from patients with cancer and compared the excretion of cholesterol with that of normal subjects and of patients afflicted with diseases other than cancer. Although hypercholesteruria was more frequent in patients with cancer, these authors said it was not pronounced enough to be called a consistent finding in association with malignant tumor. They explained the high values in some patients as possibly due to the inclusion of urine from patients with associated renal disease, who manifested hypercholesteruria because of the proteinuria.[5]

From the Medical Research Laboratory, Department of Medicine, New York Post-Graduate Medical School and Hospital, Columbia University.

1. Sobotka, H.: The Chemistry of the Sterids, Baltimore, Williams & Wilkins Company, 1938, p. 98.

2. Sobotka, H., and Bloch, E.: Urine Extractives in Cancer, Am. J. Cancer **35**:50, 1939.

3. Bloch, E., and Sobotka, H.: Urinary Cholesterol in Cancer, J. Biol. Chem. **124**:567, 1938.

4. Sobotka, H.; Bloch, E., and Rosenbloom, A. B.: Urinary Cholesterol in Cancer: II, Am. J. Cancer **38**:253, 1940.

5. Bruger, M.: Cholesteroluria in Bright's Disease, Am. J. Clin. Path. **5**:504, 1935.

METHOD AND MATERIAL

In the present investigation, twenty-four hour specimens of urine from 26 normal subjects, 28 patients with various diseases other than cancer and 32 patients with proved cancer were analyzed for cholesterol according to the procedure developed recently in this laboratory.[6] A portion of each specimen was subjected simultaneously to a routine analysis for protein, sugar, etc. On the day the urine was collected, venous blood was obtained for the determination of the plasma cholesterol content (modified Bloor procedure [7]) and of the sedimentation rate (Westergren [8]).

TABLE 1.—*The Cholesterol Content of the Urine in 26 Normal Subjects (31 Determinations)*

				Urine		
					Cholesterol *	
Subject	Age	Sex	Results of Urinalysis	Volume Cc./24 Hr.	Mg./100 Cc.	Mg./24 Hr.
1	30	M	Negative	1,030	0.07	0.76
2	23	M	Negative	1,240	0.02	0.27
3	26	M	Negative	600	0.12	0.72
4A	22	F	Negative	740	0.21	1.52
B			Negative	1,110	0.12	1.31
5	45	F	Negative	625	0.16	1.01
6	36	F	Negative	1,010	0.17	1.74
7	19	F	Negative	675	0.13	0.90
8	19	F	Trace of protein	870	0.25	2.16
9	25	F	Negative	410	0.19	0.79
10	31	M	Negative	805	0.06	0.48
11A	35	F	Negative	2,105	0.10	2.15
B			Negative	3,030	0.13	3.88
12	30	F	Negative	840	0.17	1.45
13	28	F	Negative	1,230	0.20	2.50
14	22	F	Negative	1,390	0.19	2.68
15	20	F	Faint trace of protein	730	0.20	1.46
16	27	M	Negative	1,380	0.18	2.53
17	28	M	Negative	1,510	0.15	2.28
18	28	F	Negative	680	0.32	2.21
19	25	F	Negative	605	0.41	2.49
20A	25	F	Negative	1,430	0.19	2.72
B			Negative	1,510	0.22	3.25
C			Negative	1,180	0.15	1.76
D			Negative	775	0.22	1.72
21	27	M	Negative	600	0.09	0.56
22	40	M	Negative	640	0.15	1.00
23	21	F	Negative	920	0.18	1.67
24	20	F	Negative	900	0.26	2.36
25	19	F	Occasional red blood cell	730	0.16	1.16
26	25	F	Negative	960	0.12	1.16
Range					0.02 - 0.41	0.27 - 3.88
Mean					0.17	1.69
Standard deviation					±0.07	±0.85

* The total output of cholesterol in twenty-four hours was calculated by multiplying the actual volume of urine by the concentration of urinary cholesterol per hundred cubic centimeters to three places. The volume of urine and the concentration of urinary cholesterol charted here and in tables 2 and 3 are given in round figures.

RESULTS

Table 1 shows the results for 26 normal subjects (interns, nurses, technicians and other hospital personnel) ranging in age from 19 to 45 years. The excretion of cholesterol in the urine varied from 0.27 to 3.88 mg. in twenty-four hours with a mean of 1.69 ± 0.85 mg. These values for normal subjects are appreciably higher

6. Bruger, M., and Ehrlich, S. B.: On the Determination of Urinary Cholesterol, J. Lab. & Clin. Med. **27**:1093, 1942.

7. Sackett, G. E.: Modification of Bloor's Method for the Determination of Cholesterol in Whole Blood or Blood Serum, J. Biol. Chem. **64**:203, 1925.

8. Westergren, A.: Die Senkungsreaktion; Allgemein-klinische Ergebnisse; Praktische Bedeutung bei Tuberkulose, Ergebn. d. inn. Med. u. Kinderh. **26**:577, 1924.

than those previously reported,[9] but the difference may be ascribed to the more accurate analytic procedure used in the present study.

Table 2 indicates the results obtained for 28 patients with various disorders other than cancer. It will be observed that the mean excretion of cholesterol in this group was slightly higher than that of normal subjects (2.01 mg. per twenty-four hours). For the most part, however, the individual variations fell well within the normal range. A cholesterol excretion of 4.24 mg. in twenty-four hours being considered the upper limit of normal (mean plus three times the standard deviation), only patient 4, with cirrhosis of the liver, showed an abnormally high excretion of this

TABLE 2.—*The Cholesterol Content of the Urine in 28 Patients with Various Clinical Disorders Other Than Cancer*

Patient	Age	Sex	Diagnosis	Results of Urinalysis	Sedimentation Rate Mm./Hr.	Plasma Cholesterol Mg./100 Cc.	Urine		
							Volume Cc./24 Hr.	Cholesterol Mg./100 Cc.	Cholesterol Mg./24 Hr.
1	65	M	Obstructive jaundice	7-10 WBC/HPF *	62	242	1,790	0.22	3.85
2	55	F	Pyelonephritis	Negative	53	...	975	0.14	1.34
3	37	F	Chronic diffuse glomerular nephritis	++ Protein	110	235	630	0.16	0.98
4	55	M	Cirrhosis of liver	Trace of protein	68	...	950	0.46	4.38
5	18	F	Cirrhosis of liver, juvenile	Negative	112	248	2,790	0.12	3.35
6	48	F	Cirrhosis of liver	Negative	45	137	400	0.32	1.26
7	55	M	Cirrhosis of liver	Negative	53	144	650	0.13	0.83
8	62	M	Lipoma	Negative	25	278	2,295	0.12	2.93
9	48	M	Fracture of skull	Negative	97	95	1,100	0.21	2.31
10	40	F	Acromegaly	Negative	20	...	1,210	0.27	3.28
11	76	M	Generalized arteriosclerosis	Negative	...	...	980	0.10	0.99
12	62	F	Generalized arteriosclerosis	5-10 WBC/HPF *	31	203	860	0.16	1.37
13	48	M	Generalized arteriosclerosis	Negative	23	230	1,150	0.05	0.62
14	67	M	Generalized arteriosclerosis	Negative	...	226	1,360	0.18	2.41
15	46	F	Generalized arteriosclerosis	Negative	25	206	630	0.34	2.11
16	59	F	Generalized arteriosclerosis	Negative	46	295	760	0.26	1.98
17	52	F	Rheumatic heart disease	Negative	.	...	420	0.58	2.42
18	15	F	Rheumatic heart disease	Negative	15	179	440	0.38	1.67
19	18	F	Rheumatic heart disease	Negative	10	102	630	0.28	1.76
20	24	F	Acute rheumatic fever	Many RBC	24	176	545	0.30	1.61
21	19	F	Acute tonsillitis	Negative	37	163	600	0.31	1.84
22	26	F	Chronic appendicitis	Negative	28	194	1,450	0.25	3.61
23	67	M	Herpes zoster	Negative	...	172	2,175	0.10	2.16
24	18	F	Exophthalmic goiter	Negative	40	205	325	0.33	1.07
25	61	M	Exophthalmic goiter	Negative	41	89	565	0.10	0.59
26	47	F	Exophthalmic goiter	Negative	39	180	545	0.20	1.09
27	48	F	Rheumatoid arthritis	Negative	45	144	420	0.56	2.36
28	54	F	Sciatic neuritis	Negative	...	205	900	0.25	2.21
Mean								0.25	2.01

* White blood cells per high power field.

sterol. His hypercholesteruria could be ascribed in part to the loss of protein in the urine. It will be observed further that there was little or no correlation between the sedimentation rate, the plasma cholesterol content and the degree of cholesteruria.

Table 3 details the clinical diagnosis, the diagnostic criteria, the results of routine urinalyses, the sedimentation rate and the plasma cholesterol content for 32 patients with proved cancer. The time relationship of the studies on urinary cholesterol to the duration of symptoms and to operation, death, etc., is also noted.

The occurrence of hypercholesteruria in patients with some types of cancer is shown. The excretion of cholesterol in the urine was abnormally high in 3 of 4 patients with carcinoma of the breast (patients 1, 2 and 4), in 3 of 9 with adenocarcinoma of the rectum (patients 8, 12 and 13) and in 2 of 5 with carcinoma of the

9. Sobotka, Bloch and Rosenbloom.[4] Bruger.[5]

stomach or colon (patients 16 and 18). The excretion of excessive amounts of cholesterol in the urine was independent of proteinuria, since the urine of many of these patients failed to reveal detectable quantities of protein.

In each of 6 patients with squamous or basal cell carcinoma of the skin, larynx or alveolar ridge, the excretion of cholesterol in the urine was not abnormal (patients 19 to 24). Normal values were also obtained for patients with carcinoma of the lung (patients 25 to 27), carcinoma of the bone (patient 28), primary carcinoma of the liver (patient 29), adenocarcinoma of the cervix (patient 30), papillary adenocarcinoma of the ovary (patient 31) and melanosarcoma (patient 32).

It was observed that the highest urinary values for cholesterol were obtained for patients with adenocarcinoma of the rectum (patients 8, 12 and 13). This may have been a fortuitous observation because of the fewness of the patients studied, but such values as 27.9, 19.7 and 47.8 mg. in twenty-four hours are unusual. Of interest was the observation that in 2 of the patients for whom serial determinations were carried out the urinary cholesterol decreased as the disease progressed (patients 12 and 13). No correlation was observed between the sedimentation rate, the plasma cholesterol content and the degree of cholesteruria in these patients.

COMMENT

Hypercholesteruria is frequently encountered in patients with nephritis, particularly in those exhibiting a nephrotic component because of the associated loss of protein in the urine. The increased excretion of urinary cholesterol in these patients may be explained by the chemotactic relationship existing between protein and cholesterol. On the other hand, since cholesterol may exist in the blood as large molecular aggregates approximating the protein molecule in size, both cholesterol and protein may filter through the pathologically permeable glomerulus.[10] Whichever hypothesis is correct, in patients with Bright's disease the excretion of cholesterol in the urine parallels the loss of protein.[5]

In some patients with cancer, however, large amounts of cholesterol may be excreted in the urine without any evidence of increased glomerular permeability (little or no proteinuria). It is rather difficult to explain this phenomenon unless one assumes that the cholesterol released into the blood stream by disintegrating malignant tumors is physicochemically different from the cholesterol normally present in the plasma. Thus, if the sterols released by cancer tissue exist as single molecules or as micellae, diffusion through a normal glomerular membrane may be possible. It may be stated here, however, that many experiments carried out in this laboratory have to date failed to reveal any abnormal physicochemical status of the plasma cholesterol in patients with cancer. This phase of the problem is still being investigated.

Though hypercholesteruria is frequently encountered in patients with cancer, it is not an invariable finding. This, too, is rather difficult to explain. Obviously, much more investigation is required. A prolonged study on a large number of patients may prove fruitful if planned to include such observations as a correlation of the cholesteruria to the type, grade and duration of the cancer, to the presence or absence of metastases, to the effect of roentgen ray and radium therapy, to the results of surgical removal of the tumor and, finally, to the cholesterol content of the malignant tissue.

10. Bruger, M.: The State of Cholesterol and the Nature of the Cholesterol-Protein Complex in Pathological Body Fluids, J. Biol. Chem. **108**:463, 1935.

TABLE 3.—*The Cholesterol Content of the Urine in 32 Patients with Proved Cancer (36 Determinations)*

Patient	Age	Sex	Diagnosis	Duration of Symptoms Months	Diagnostic Criteria	Results of Urinalysis	Sedimentation Rate Mm./Hr.	Plasma Cholesterol Mg./100 Cc.	Urine			Time Relationship *
									Volume Cc./24 Hr.	Cholesterol Mg./100 Cc.	Cholesterol Mg./24 Hr.	
1	71	F	Adenocarcinoma of left breast	4	Pathologic changes in tissue	15 WBC/HPF †	115	...	1,550	0.55	8.56	1½ months after radical left mastectomy
2	30	F	Adenocarcinoma of right breast	2	Pathologic changes in tissue	Negative	92	207	1,438	0.41	5.82	8 days after radical right mastectomy
3	40	F	Adenocarcinoma of left breast	6	Pathologic changes in tissue	Negative	35	276	565	0.39	2.18	7 weeks after radical left mastectomy
4	52	F	Scirrhous carcinoma of left breast	1	Pathologic changes in tissue	Negative	67	244	950	0.65	6.15	4 days after radical left mastectomy
5	43	M	Adenocarcinoma of rectum and sigmoid flexure	12	Pathologic changes in tissue	Negative	18	...	785	0.19	1.45	7 months after abdominal perineal resection
6	54	F	Adenocarcinoma of rectum	1½	Pathologic changes in tissue	Trace of sugar	38	236	3,430	0.08	2.64	Simultaneous with operation
7	37	M	Adenocarcinoma of rectum	3	Pathologic changes in tissue	Negative	140	291	900	0.23	2.07	Simultaneous with operation
8	59	F	Adenocarcinoma of rectum	12	Pathologic changes in tissue	Trace of protein, 0.5% sugar, many red blood cells	55	203	1,950	1.43	27.89	2½ months after colostomy
9	45	M	Adenocarcinoma of rectum	12	Pathologic changes in tissue	Negative	...	...	1,890	0.10	1.89	1½ years after abdominal perineal resection
10	48	F	Adenocarcinoma of rectum	5	Pathologic changes in tissue	Negative	...	223	2,550	0.09	2.40	7 months after abdominal perineal resection
11A	75	M	Adenocarcinoma of rectum	72	Pathologic changes in tissue	Negative	...	...	850	0.25	2.10	3 years after colostomy
B						Negative	18	148	1,270	0.14	1.74	Urinalysis 2 months later; death 2 months after this study
12A	62	M	Adenocarcinoma of rectum	7	Pathologic changes in tissue	Trace of protein, many red blood cells	47	...	4,425	0.45	19.74	11 days after colostomy
B						Negative	...	165	1,840	0.20	3.66	Urinalysis 3½ months later
13A	50	F	Adenocarcinoma of rectum	12	Pathologic changes in tissue	Negative	143	123	2,740	1.75	47.82	1 week after abdominal perineal resection
B						Negative	124	200	2,700	0.77	20.68	Urinalysis 14 days later
C						Trace of protein, 5-10 WBC/HPF	...	180	1,850	0.52	9.64	Urinalysis 4 months later
14	51	F	Abdominal carcinomatosis (metastatic)	1	Pathologic changes in tissue	Negative	38	...	540	0.34	1.83	Death 5 days later

15	63	F	Carcinoma of stomach and lower end of esophagus	6	Macroscopic pathologic changes (operation)	Negative	41	233	177	0.77	1.30	Simultaneous with operation
16	39	M	Carcinoma of stomach with metastases to mesenteric lymph nodes	2	Pathologic changes in tissue	Negative	9	214	1,275	0.41	5.18	12½ days before an exploratory laparotomy; death 5 days later
17	61	F	Adenocarcinoma of transverse colon and sigmoid flexure	?	Pathologic changes in tissue	Negative	93	262	830	0.40	3.29	6 months after exploratory laparotomy
18	52	M	Adenocarcinoma of colon	3	Pathologic changes in tissue	Trace of sugar, numerous white blood cells	29	172	1,800	0.46	8.35	1½ months after ileocolectomy
19	57	M	Squamous cell carcinoma of cheek	12	Pathologic changes in tissue	Negative	47	248	600	0.28	1.65	1 week after dissection and plastic repair
20	56	M	Squamous cell carcinoma of larynx	2	Pathologic changes in tissue	Negative	26	...	1,100	0.24	2.66	2 days after tracheotomy and direct laryngoscopy with biopsy
21	59	M	Squamous cell carcinoma of upper alveolar ridge	12	Pathologic changes in tissue	Negative	106	199	410	0.22	0.88	3 days after electrocoagulation and endothermic excision
22	57	M	Basal cell carcinoma of skin	108	Pathologic changes in tissue	6-7 WBC/HPF	49	230	1,580	0.13	2.02	1 month after excision and plastic repair
23	51	M	Basal cell carcinoma of skin	48	Pathologic changes in tissue	Negative	40	217	2,140	0.14	2.80	2 days after excision and plastic repair
24	70	M	Squamous cell carcinoma of mouth	12	Pathologic changes in tissue	Negative	85	165	1,450	0.15	2.18	
25	50	F	Carcinoma of lung (secondary)	6	Roentgenologic changes	Negative	40	191	340	0.86	2.91	4 years after radical left mastectomy
26	50	F	Carcinoma of lung (secondary)	12	Roentgenologic changes	Negative	40	171	1,450	0.19	2.72	12 years after radical left mastectomy
27	57	F	Carcinoma of lung (primary)	24	Roentgenologic changes	10-20WBC/HPF	98	172	920	0.32	2.96	
28	39	M	Carcinoma of right humerus and second lumbar vertebra (metastatic)	4	Roentgenologic changes	Negative	33	193	830	0.14	1.19	
29	47	F	Carcinoma of liver (primary)	9	Pathologic changes in tissue	Negative	95	232	880	0.23	2.06	2 weeks after punch biopsy; death 4 weeks later
30	21	F	Adenocarcinoma of cervix	?	Pathologic changes in tissue	Negative	39	218	590	0.66	3.91	4 days after uterine curettage
31	66	F	Papillary adenocarcinoma of right ovary with metastases to abdominal viscera	2	Pathologic changes in tissue	+ Protein, 5-10 WBC/HPF	48	109	380	0.20	0.76	Death 1 day later
32	43	M	Melanosarcoma (metastatic)	1	Pathologic changes in tissue	Negative	109	...	1,860	0.22	4.15	2 weeks after resection of bilateral inguinal node
Mean										0.40	6.09	

* Time relationship between determination of urinary cholesterol and operation, death, etc.
† White blood cells per high power field.

SUMMARY AND CONCLUSIONS

The excretion of cholesterol in the urine in 26 normal subjects ranged from 0.27 to 3.88 mg. in twenty-four hours with a mean of 1.69 ± 0.85 mg. In 28 patients with a variety of clinical disorders other than cancer, the mean excretion of cholesterol was slightly higher than in normal subjects (2.01 mg. in twenty-four hours), but for the most part the individual variations fell well within the normal range. In 8 of 32 patients with cancer, the excretion of cholesterol in the urine was significantly elevated above normal; the highest value noted was 47.8 mg. in twenty-four hours in a patient with adenocarcinoma of the rectum. The mean amount of urinary cholesterol for this group was 6.09 mg. in twenty-four hours. No correlation was observed between the sedimentation rate, the plasma cholesterol content and the degree of cholesteruria. Hypercholesteruria occurs independently of loss of protein in the urine; some theoretic considerations are offered to account for this phenomenon.

301 East Twentieth Street.

Progress in Internal Medicine

BLOOD

A REVIEW OF THE RECENT LITERATURE

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(Continued from Page 903)

APLASTIC ANEMIA AND REFRACTORY ANEMIAS

No new and important information concerning aplastic anemia was reported in 1942, with the possible exception that the condition may follow the use of sulfathiazole. A paper by Vaughan [180] deals with 34 cases of aplastic anemia, both of the primary and of the secondary type. He quotes Rosenthal as stating that the disease may be defined as a progressive condition of unknown cause characterized by severe anemia, leukopenia, thrombopenia and marrow acellularity. When it does not conform to this description, it is regarded as atypical. The cases in which a cause for the disease can be ascertained are segregated as cases of the secondary type. Vaughan considers aplastic anemia in the broader sense, which includes the two subgroups indicated. Ten of the cases were of the secondary type; in 6 of these the anemia was due to arsphenamine, and in 4, to benzene. The remaining cases were regarded as instances of the cryptogenic variety of aplastic anemia, although in 2 there was toxemia of pregnancy and in 1 miliary tuberculosis. The author emphasizes that accurate classification is highly desirable but by no means simple, as adequate means for making a differentiation are not always available. Moreover, the history of exposure is not always easy to interpret. The symptoms and signs in this group were those usually observed, with the following exceptions: In 34 per cent of the patients there was some degree of enlargement of the lymph nodes clinically; 15 per cent had enlargement of both the lymph nodes and the spleen, and 12 per cent had enlargement of the lymph nodes, the spleen and the liver. These clinical observations were substantiated by necropsies. In a great majority of the cases the classic findings of severe anemia, leukopenia and thrombopenia were present. In 27 per cent the anemia was macrocytic, in 54 per cent normocytic and in 19 per cent microcytic. In only a single instance was achlorhydria present, and that was a case of macrocytic anemia. Usually there was a reduction in the number of mature polymorphonuclear cells, with relative lymphocytosis. Bone marrow was obtained in 26 of the 34 cases—either during life, by sternal puncture or by trephination, or at necropsy, by the usual technic. In some instances both antemortem and postmortem observations were made. In 12 of the cases the marrow showed a remarkable reduction of cellularity; in 8 there was much greater cellu-

180. Vaughan, S. L.: Aplastic Anemia, New York State J. Med. **42**:978, 1942.

larity, with variation in appearance in the sections obtained from different areas; in 2 there seemed to be distinct hyperplasia, and in 1 hypoplasia, which did not reach the degree of acellularity previously described.

The general findings in the 14 cases which came to necropsy were as follows: in 5 cases, splenomegaly, which was an outstanding feature in 2 cases; in 4, hepatomegaly; in 7, bronchopneumonia, and in 2, pleuritis. In 10 cases diffuse hemorrhagic phenomena were present, and in 3 these phenomena seemed to be the most pronounced of the terminal features. In 3 cases ulcerative lesions with or without sepsis were present, and in 1 case this was the most conspicuous feature.

The outcome of the disease in the 34 cases was as follows: complete recovery in 15 per cent; death in 73 per cent; result pending in 12 per cent. The results indicate the extremely high mortality of the series as a whole, and a somewhat better outlook in cases of the secondary as opposed to cases of the cryptogenic type.

The following eleven agents were employed in treatment: blood by transfusion and by intramuscular injection, iron, liver products, vitamins, yellow bone marrow, pentnucleotide (the sodium salts of pentose nucleotides from the ribonucleic acid of yeast), roentgen rays, ultraviolet rays, endoglobulin, sulfonamide compounds, and marrow by transfusion; in addition, splenectomy and uterine curettement were performed. Of the measures mentioned, only blood transfusions were used in all the cases. The author concludes that in some cases they have been instrumental in prolonging life until a remission could occur. The study led the author to conclude that aplastic anemia should be regarded as a disorder of varied manifestations in which the fundamental defect is one of general hemopoietic insufficiency varying from inhibition of normal maturation and distribution of cells to actual hyperplastic changes.

Meyer and Perlmutter[181] emphasize that the untoward hematologic changes following the use of the sulfonamide compounds fall into two main groups, namely, agranulocytosis and hemolytic anemia, but that leukemoid reactions and thrombopenic purpura have also been observed. According to the authors, their case is the first one of aplastic anemia due to the use of such drugs to be reported. The patient was a 55 year old Assyrian woman in whom bronchopneumonia developed and who was given 12 Gm. of sulfathiazole over a period of two days. At the end of that time, on admission to the hospital the blood findings were as follows: hemoglobin, 5 Gm.; red blood cell count, 1,710,000 per cubic millimeter; white blood count 1,000, with polymorphonuclears 8 per cent, lymphocytes 88 per cent, monocytes 4 per cent and platelets none. Sternal marrow obtained by aspiration showed hypoplasia with suppression of the cellular components. With cessation of the administration of sulfathiazole and with blood transfusions and injections of liver extract and pentnucleotide there was a rapid rise in the blood platelet count, the hemoglobin level and the number of red and white blood cells. At the time of death, twenty-two days after admission, the hemoglobin value was 7.0 Gm., the red blood cell count 1,600,000 and the white blood cell count 20,500, with 38 per cent polymorphonuclear cells; only rare platelets were present. A second sternal puncture, made six days after the initial one, is stated to have yielded an "essentially normal differential smear." Postmortem sections of the marrow showed moderate hyperplasia, with all of the usual cellular elements present. The authors emphasize that the aplastic picture was evident after the administration of only 12 Gm. of the sulfonamide compound over a period of two

181. Meyer, L. M., and Perlmutter, M.: Aplastic Anemia Due to Sulfathiazole, J. A. M. A. **119**:558 (June 13) 1942.

days and that the case shows that the marrow may return to normal with discontinuance of the administration of the drug. No mention is made of previous medication with sulfonamide compounds which might have sensitized the patient to subsequent doses. In the absence of sensitization it is remarkable that such a serious dyscrasia of the blood should develop following such a small total dose. Furthermore, it is not established with certainty that the aplastic anemia in this patient was actually a result of the medication, as such a condition due to an unknown cause may have been present independently and concurrently.

An unusual case of aplastic anemia, in which the organs at necropsy showed the changes of hemochromatosis, is presented by Mackey.[182] The patient, a laborer aged 46 years, had the disease for three and one-half years, during which time he received thirty-nine blood transfusions. At one time, for a short interval, he felt so well that he presented himself to the hospital as a donor. At this time the red blood cell count and the hemoglobin content were within normal limits. The period of remission, however, was brief, as a blood transfusion was required a short time later. It was suggested that the changes characteristic of hemochromatosis may have been due to storage of iron in the various tissues, as the body was unable to utilize it in the formation of hemoglobin.

Hurwitt and Field[106] observed the case of a 27 year old woman who died in the fourteenth week of pregnancy of severe anemia which had all the characteristics of the so-called idiopathic aplastic type. In a group of 14 cases of aplastic anemia occurring during pregnancy, which were collected from the literature, there were only 5 in which the patient survived. In all of these, the uterus had been emptied, by normal delivery in 2 and by interruption during the third trimester in 2. In 1 case the disease developed post partum. They believe that the association of this variety of anemia with pregnancy is more than coincidental; in other words, that the gravidity may play an etiologic or a conditioning role. They advise that in the presence of this variety of anemia interruption of the pregnancy be strongly considered.

Sterne[183] reports the case of a 39 year old white man who had a red blood cell count of 1,500,000 per cubic millimeter, a hemoglobin value of 5.3 Gm., a white blood cell count of 1,350, with 30 per cent neutrophils, and a platelet count of 12,200. The differential diagnosis rested between subleukemic leukemia and panhypoplasia of the marrow due to treatment with neoarsphenamine. The absence of pathologic leukocytes in the circulating blood ruled out the former, and aspirated marrow showed the characteristic picture of the latter. Of the four methods of therapy, transfusion of blood, injection of pentnucleotide, administration of yellow bone marrow and intrasternal infusion of the marrow, the first mentioned is regarded as the most satisfactory by the author.

The case of an Italian aged 50 years in whom severe aplastic anemia developed during the course of six injections of neoarsphenamine is reported by Sayer.[184] Examination of his blood showed the hemoglobin content 35 per cent of normal and the red blood cells 1,500,000, the white blood cells 2,200 and the platelets 40,000 per cubic millimeter. Recovery followed injections of pentnucleotide and repeated blood transfusions.

182. Mackey, R.: An Unusual Case of Aplastic Anemia with Organ Changes Resembling Haemochromatosis, M. J. Australia **1**:172, 1942.

183. Sterne, E. H., Jr.: Leukopenia and Anemia After Therapy: Differential Diagnosis, Cincinnati J. Med. **23**:173, 1942.

184. Sayer, A.: Aplastic Anemia Due to Arsphenamine; Stomatitis of Unknown Origin, Arch. Dermat. & Syph. **46**:453 (Sept.) 1942.

A case of aplastic anemia is reported by Meyer and Ginsberg [185] in which there was a period of ten years between the exposure to benzene and the development of symptoms. The history and physical findings were typical of this type of anemia, and the case terminated fatally fourteen days after the patient's admission to the hospital. The diagnosis was verified by necropsy. There does not seem to be any doubt that the patient was extensively exposed to benzene ten years before the development of symptoms, and it is likewise clear that he succumbed to the condition which we call aplastic anemia. But there is no evidence to indicate that the benzene played a role in the causation of the disease inasmuch as the same condition may develop without a recognizable cause.

Beizer and Watkins [186] report their findings from examination of sternal marrow obtained by aspiration in 12 cases of refractory anemia in which the clinical picture was that of aplastic anemia. Cases in which there was evidence of depression of the activity of the marrow and of relative lymphocytosis followed the usual clinical course, with death occurring in a relatively short time. On the other hand, cases with evidence of hyperplasia of the marrow but with no observable lymphocytosis did not terminate fatally.

GRANULOCYTOPENIA AND AGRANULOCYTOSIS

The literature in 1942 includes reports of cases of agranulocytosis following the administration of sulfanilamide, sulfapyridine and sulfadiazine (2-[paraaminobenzenesulfonamido]-pyrimidine). When the widespread use of these drugs is considered, the incidence of this grave complication does not seem great. It is now thought that the persons in whom agranulocytosis develops are sensitized to the drugs or become sensitized to them during the course of therapy. Controversy continues concerning the treatment of this disorder. It is of interest to note that opinion seems to favor the employment of sulfonamide drugs as therapeutic agents if the syndrome of agranulocytosis has not been induced by them.

Metzger,[187] in a memorial to Philip King Brown, records the little known fact that the latter was the first to describe the syndrome of agranulocytosis in an article published in 1902 in *American Medicine*, volume 3, page 649, entitled "A Fatal Case of Acute Primary Infectious Pharyngitis with Extreme Leukopenia." Thus, twenty years before Werner Schultz published his classic paper dealing with the disease Brown had described this condition accurately and completely, as any one can determine by consulting his original paper.

Henry Jackson Jr., in a review [188] of the current literature dealing with agranulocytosis, expresses himself rather positively on several controversial points. He agrees that in the great majority of cases this disease is secondary to the action of some drug but is inclined to believe that there are a few instances in which it is truly idiopathic. Such cases, in the opinion of the author, are exceedingly rare and are becoming more so as knowledge of the malady increases. He also believes that severe neutropenia, indistinguishable from classic agranulocytosis, may be secondary to overwhelming sepsis. According to him, it is difficult, if not impossible, to distinguish between idiopathic agranulocytosis and the leukopenia that is

185. Meyer, L. M., and Ginsberg, V.: Aplastic Anemia, J. Indust. Hyg. & Toxicol. **24**: 37, 1942.

186. Beizer, L. H., and Watkins, C. H.: Sternal Marrow in Aplastic Anemia, J. Clin. Investigation **21**:636, 1942.

187. Metzger, J.: Philip King Brown, M. D., Tr. Am. Clin. & Climatol. A. (1941) **57**:xlv, 1942.

188. Jackson, H., Jr.: Medical Progress: Leukopenia; Agranulocytosis, New England J. Med. **225**:978, 1941.

due to the action of certain drugs, overwhelming sepsis or industrial poisoning. (In our opinion, true agranulocytic angina may sometimes be differentiated from the neutropenia of sepsis, because the latter rarely is associated with complete absence of neutrophils from the blood stream, which rarely make up less than 10 per cent of the leukocytes. Complete absence of neutrophils commonly occurs in true agranulocytosis.) It is emphasized that at present aminopyrine is less commonly provocative of the malady, because its dangers are now widely recognized, and in some countries its sale is limited by law. Gold preparations may occasionally cause the condition, and there is an ever increasing number of cases of grave granulocytopenia due to the sulfonamide compounds. In the author's opinion, it is probable that any of these preparations may be responsible for the disease. In a series of 109 collected cases he found the causative agents to be as follows: sulfanilamide in 34, sulfapyridine in 8, aminopyrine alone in 39, allonal (allylisopropylbarbituric acid with aminopyrine [before 1939] or acetophenetidin [since 1939]) in 7 and causalin (aminodimethylpyrazolon quinoline sulfonate) in 4. In decreasing frequency, the following drugs were considered to be causative: cibalgine (aminopyrine and a barbital derivative [dial]), acetanilid, amidophen (aminopyrine, acetophenetidin, caffeine and extract of hyoscyamus), cinchophen, amytal compound (amytal and aminopyrine), bismarsen and neocinchophen. Jackson acknowledges that the treatment of the disorder still remains a matter of debate. He makes a number of excellent points, however, with which we are in entire agreement, concerning the administration or the continuation of the use of sulfonamide compounds in the presence of extreme leukopenia; thus, if the latter condition is obviously due to the drug, it should be stopped immediately, but if it is secondary to an infection which ordinarily is amenable to treatment with the sulfonamide compounds, these therapeutic agents should at once be given along with pentnucleotide, in an attempt to restore the leukocyte count to normal. Jackson contends rather strongly that the mere withdrawal of the offending drug does not always suffice to restore the white blood cell picture to normal, and hence other measures, such as the administration of pentnucleotide, should be employed. In support of this view Jackson cites his observations on 72 personally collected cases of agranulocytosis due to sulfonamide compounds or other drugs, in 30 per cent of which recovery followed the withdrawal of the drug without other specific medication. Of 26 similar cases in which the drug was withdrawn and adequate amounts of pentnucleotide were given (40 cc. daily), recovery occurred in 66 per cent. Jackson gives a timely warning that all patients who are under treatment with drugs known to cause the condition should have frequent leukocyte and differential counts. If the total granulocyte count is found to be low, administration of the drug should be stopped and intensive treatment instituted at once, whether one chooses to treat by injections of pentnucleotide, frequent blood transfusions, administration of yellow bone marrow or a combination of these measures. He states, as previously, that if pentnucleotide is given, not less than 40 cc. should be administered daily, and its use should be continued until a favorable response has occurred or until it is apparent that no benefit will occur.

With a sweeping and to us unjustified statement, Dameshek and Wolfson [189] cast aside as worthless practically all forms of therapy which have been introduced in connection with agranulocytosis. Included in this relegation are the pentose nucleotides, adenine sulfate, liver extract, transfused blood and yellow bone marrow

189. Dameshek, W., and Wolfson, L. E.: A Preliminary Report on the Treatment of Agranulocytosis with Sulfathiazole, Am. J. M. Sc. **203**:819, 1942.

extract. In our opinion their statement is unsupported, to say the least, and is not in accord with the experience of a majority of those who have had to deal with this disease. On the other hand, the authors make a point well worth while when they emphasize that death probably results from overwhelming sepsis in a body stripped of its defensive granulocytes. They treated 2 patients for severe agranulocytosis with blood transfusion and administration of pentose nucleotides, liver extract and sulfathiazole in large doses. The recovery in each case is attributed in part at least to the effect of the sulfonamide compound on the sepsis. Physicians are reluctant to give these drugs in the presence of leukopenia because occasionally agranulocytosis may develop in association with such therapy. Long and Bliss reported in 1939 that when leukopenia is due to an infectious process no harm will result from the use of a sulfonamide compound and that with this therapy the infection may be overcome, with subsequent increase in the leukocyte count and recovery of the patient. After careful consideration of the problem we concur in this opinion, for it does not follow that when leukopenia results from one cause, such as the effects of a drug, a patient will be sensitive in the same manner to another substance with which that drug has not even a remote chemical relationship. Furthermore, as the authors have emphasized, sepsis associated with agranulocytosis is one of the major problems and is the condition which ordinarily leads to the fatal issue. As the sulfonamide compounds are now the agents most effective against infection, particularly of the sort observed in association with agranulocytosis, their possible beneficial effect should not be denied to the patient.

Barsby and Close [190] state that Beck in 1933 classified agranulocytosis as of five types: fulminating, subacute, subchronic, recurrent and cyclic. They state, however, that the classification is unsatisfactory because some patients show the characteristic symptoms of more than one type. They report the case of a woman of 41 years who had pyrexial attacks with sore throat, ulcers of the mouth, a pink rash, pains in the joints, cough, abdominal pain and vomiting. These episodes had occurred three to seven days after her menstrual periods over an interval of four years. For the last seven months at least of the patient's illness these attacks were associated with neutrophil agranulocytosis. Only twice during the period of observation was the number of polymorphonuclear cells greater than 3,000 per cubic millimeter; on five occasions they disappeared entirely for four or five days. Necropsy disclosed pericecal inflammation and pulmonary abscess; no cause for the blood changes could be found. The fact that the condition was recurrent and seemed related to the menstrual periods would lead us to suspect strongly that the patient had been taking some drug, such as aminopyrine. In fact, after the patient's death it was discovered that she had been taking "Yeast-Vite," but this was considered as not a likely cause of the condition because the attacks were intermittent and because, according to the authors, this preparation has not contained aminopyrine since 1935. Neither objection, however, includes with certainty aminopyrine or a related compound as the significant etiologic factor.

Schackle [191] refers to the case described by Barsby and Close and records from memory a similar illness in a child aged 5 whom he observed sixteen years ago. This child experienced attacks of pyrexia at monthly intervals, each accompanied by more or less complete absence of polymorphonuclear cells from the circulation. It was possible to predict the acute febrile rise by the preceding

190. Barsby, B. E., and Close, H. G.: Recurrent Neutrophil Agranulocytosis, Lancet **1**:99, 1942.

191. Shackle, J. W.: Recurrent Neutrophilic Agranulocytosis, Lancet **1**:306, 1942.

reduction of these cells in the blood. Blood transfusions seemed to be of benefit, but the condition finally terminated fatally. Permission for necropsy was not obtained.

Waugh [192] gives a review of the changes which may occur in the blood following the introduction into the body of certain chemicals and drugs. He states that various substances may affect all of the hemopoietic activities of the marrow, producing a disorder which he calls "panmyelotoxicosis." Among these are arsenic, arsphenamine, bismuth, aminopyrine and other benzene ring derivatives. Moreover, similar paralytic effects may be produced by various forms of radiation, such as the roentgen ray, radium and thorium, either after therapy or when poisoning has occurred. He emphasizes that sulfanilamide may produce granulocytopenia, and that this may result from a small amount of the drug, as indicated in 1 case in which death occurred following the administration of only 8 Gm. In general, however, it is his belief that although the quantity given seems to make a difference, individual susceptibility is probably even more important. Two deaths following the use of sulfonamide compounds were noted in the department of pathology of McGill University. He reports that the marrow almost always reveals a characteristic deficiency in maturing myelocytes and that the immature root cells and syncytial reticuloendothelial elements are unusually conspicuous. He expresses the view that future investigations may disclose that the action of these drugs is not toxic paralysis but deficiency paralysis due to removal of some important substance necessary for the maturation of the proliferating elements of the marrow. In the treatment of agranulocytosis he recommends transfusions of blood, administration of pentose nucleotides and recognition and withdrawal of the causative agent.

Three cases of granulocytopenia, 1 in which it was due to sulfanilamide and 2 in which it was due to sulfathiazole, are reported by Carley and Reid.[193] One of the patients who received sulfathiazole succumbed.

Fatal agranulocytosis following the use of sulfathiazole in a man aged 58 years is reported by Thompson.[194] The patient had been ill at home for two weeks with an infection of the respiratory tract and was treated for this with an unknown amount of the drug. After his admission to the hospital, the administration of the drug was resumed at the rate of 45 grains (2.91 Gm.) daily until he had received a total dose of 235 grains (15.23 Gm.). In addition, over this same period approximately 160 grains (10.36 Gm.) of acetylsalicylic acid was given. The minimum white blood cell count was 100 per cubic millimeter, all of which were lymphocytes. The sternal marrow was interpreted as typical of aplastic anemia. Data regarding the hemoglobin content of the circulating blood and the red blood cell count are not given. The author expresses the opinion that the incidence of agranulocytosis is very low in proportion to the number of patients receiving sulfathiazole but that it is a complication which should be kept in mind nevertheless and one which should be guarded against by repeated blood counts.

Cross [195] presents the case of a man aged 20 in whom agranulocytosis developed, with a minimum leukocyte count of 1,000 per cubic millimeter and no polymorphonuclear leukocytes, following the administration of 42 Gm. of sulfapyridine over a

192. Waugh, T. R.: Hematologic Aspects of Chemotherapy, Arch. Otolaryng. **35**:990 (June) 1942.

193. Carley, P. S., and Reid, P. E.: Granulocytopenia Resulting from Sulfonamide (Sulfanilamide and Its Derivative, Sulfathiazole) Therapy: Case Reports and Discussion, Urol. & Cutan. Rev. **46**:19, 1942.

194. Thompson, L.: Agranulocytosis Due to Sulfathiazole, Northwest Med. **41**:133, 1942.

195. Cross, R. M.: Recovery from Agranulocytosis After a Rigor During Transfusion, Lancet **1**:9, 1942.

period of ten days. Treatment was by injections of pentnucleotide and repeated blood transfusions. During the course of the last transfusion the patient, for no known reason, experienced a severe rigor lasting for about fifteen minutes. Blood films taken immediately thereafter showed a slight increase in the total number of leukocytes and in the percentage of neutrophils. Four hours later, however, there was an increase to 40,000 per cubic millimeter, 85 per cent of which were neutrophils, most of them immature. The patient's temperature rose to 105.6 F. shortly after the chill, but the next morning it became and remained normal. Complete recovery followed. The suggestion is made that as the rigor and fever seemed to terminate the course of the agranulocytosis abruptly, induced and controlled hyperpyrexia, such as that caused by protein shock, might be useful in aborting attacks of this disease.

A fatal case of agranulocytosis following the administration of sulfapyridine for nonvenereal urethritis is reported by Conti.[196] The author warns that although the majority of reactions following the use of the sulfonamide compounds are nonfatal and transient, each patient receiving such therapy should be under close supervision, as severe reactions, such as agranulocytosis and hemolytic anemia, do occur. The patient whose case was the subject of report received a total of 405 grains (26.24 Gm.) of sulfapyridine over a period of six days. After a latent period of two weeks, fever and chills appeared, and the red blood cell count was found to be 3,280,000 per cubic millimeter; the white blood cell count was 1,900 per cubic millimeter, with 98 per cent lymphocytes, 2 per cent monocytes and no neutrophils. The patient died on the fourth day of observation, at which time the white blood cell count was 11,600, with 25 per cent blast cells, 5 per cent premyelocytes and 20 per cent myelocytes. No necropsy was performed, nor was a sternal puncture done. The unusual blood picture just before death, as well as the unexplained latent period of two weeks, raises in our opinion the possibility that the patient may have succumbed to an acute form of leukemia rather than to agranulocytosis.

Jobin [197] presents the case of a man aged 23 who had severe agranulocytosis following two courses of sulfapyridine therapy for an abscess of the lung. Some confusion arises, however, concerning the cause in this case, for with each course of sulfapyridine therapy the patient was also given allonal. No statement is made whether the latter preparation was the older type which contained aminopyrine (before 1939) or the more recent combination in which this drug has been replaced by acetophenetidin (since 1939).

Levin and Bethell [198] report the first case in the literature of agranulocytosis that was undoubtedly due to sulfadiazine. Leukopenia following the use of this drug had been previously noted. The authors emphasize that other sulfonamide compounds are known to be responsible for agranulocytosis, that although granulocytopenia usually develops after prolonged use of the drug, it may occur after administration of a small dose, and that the concentration of the sulfanilamide derivative in the blood gives no indication of the likelihood of ensuing granulocytopenia. It is their opinion that patients in whom this condition develops must be assumed to have had a preexisting idiosyncrasy for the drug or to have acquired such an idiosyncrasy during the course of its administration. The case reported

196. Conti, M. E.: Malignant Granulocytopenia Following Sulfapyridine Therapy: Case, U. S. Nav. M. Bull. **40**:165, 1942.

197. Jobin, J. B.: Agranulocytosis Following Sulfapyridine (Sulfanilamide Derivative) and Allonal Therapy: Case, Laval méd. **7**:191, 1942.

198. Levin, M., and Bethell, F. H.: Fatal Granulocytopenia Developing During Administration of Sulfadiazine (Sulfanilamide Derivative), Univ. Hosp. Bull., Ann Arbor **8**:30, 1942.

by the authors was that of a man of 70 years who had undergone resection of a gangrenous ileum in a strangulated right inguinal hernia twenty-seven days prior to his death. He received a total of 76 Gm. of sulfadiazine during a period of nineteen days. On the eighteenth day, the red blood cell count was 4,400,000 per cubic millimeter, the hemoglobin content was 11.5 Gm. per hundred cubic centimeters, the blood platelet count was 140,800 per cubic millimeter and the white blood cell count was 850 per cubic millimeter, with 2 per cent polymorphonuclears. The sternal marrow showed myeloblasts and early myelocytes, with little evidence of maturation beyond the myelocyte stage.

Curry [199] reports the case of a 41 year old woman in whom acute agranulocytosis developed, with a minimum white blood cell count of 650 per cubic millimeter and complete absence of polymorphonuclear leukocytes, following the administration of sulfadiazine. The patient had a diagnosis of portal cirrhosis with acute hepatitis and was given the drug on the ninth day in the hospital because of fever and roentgen evidence of bronchopneumonia. In all, the patient received 140 Gm. over a period of twenty-three days at the approximate rate of 6 Gm. a day. At the time of the development of the agranulocytosis the concentration of sulfadiazine in the blood had reached 28.3 mg. per hundred cubic centimeters. Recovery followed discontinuance of the drug, administration of pentnucleotide and transfusions of blood.

In a discussion [200] before the Section of Laryngology of the Royal Society of Medicine on involvements of the throat and nose in diseases of the blood, agranulocytosis is mentioned along with hemophilia, Osler's disease (hemorrhagic telangiectasia), leukemia, achlorhydric anemia, avitaminosis and glandular fever.

Spicer and his associates [201] have made the important observation that when rats are given sulfaguanidine (sulfanilylguanidine) or sulfasuxidine (succinylsulfathiazole) in purified diets they show granulocytopenia or agranulocytosis and hypocellularity of the bone marrow. This condition can be largely prevented or treated successfully with dried whole liver or with certain liver extracts. In addition, the rate of growth of young rats is diminished, and occasionally anemia develops. The usual change in the blood, however, is a reduction in the total number of leukocytes with a decrease in the granulocytes, commonly to below 10 per cent. It has been suggested that these drugs produce the aforementioned effects by lowering the intestinal synthesis of certain factors essential to growth, or by direct toxic action or possibly by interference with the functioning of one or more enzyme systems in the animal body. The investigators conclude that it is possible that the direct toxicity, the indirect toxicity and the lowering of intestinal synthesis may all be involved. Beding [202] gives a critical review of present knowledge bearing on the problem of agranulocytosis.

INFECTIOUS MONONUCLEOSIS

Several important articles dealing with infectious mononucleosis have recently appeared, in which previous reports suggesting a virus as the etiologic agent are confirmed. In other publications it is urged that as the condition has many diverse

199. Curry, J. J.: Acute Agranulocytosis Following Sulfadiazine, J. A. M. A. **119**:1502 (Aug. 29) 1942.

200. Mollison, W. M., and MacFarlane, R. G.: Discussion on Throat and Nose Manifestations of Blood Disease, Proc. Roy. Soc. Med. **35**:401, 1942.

201. Spicer, S. S.; Daft, F. S.; Sebrell, W. H., and Ashburn, L. L.: Prevention and Treatment of Agranulocytosis and Leukopenia in Rats Given Sulfanilylguanidine or Succinyl Sulfathiazole in Purified Diets, Pub. Health Rep. **57**:1559, 1942.

202. Beding, A.: Kritische Uebersicht über den leutigen Stand der Agranulozytose-probleme, Med. Klin. **38**:733, 1942.

manifestations the diagnosis must be based on the appearance of the characteristic lymphocytes in the blood and a positive antibody reaction against sheep cells, that jaundice, conjunctivitis and sometimes abdominal pain simulating acute appendicitis may appear as complications and that sulfathiazole and convalescent serum may be helpful therapeutic agents.

Nettleship [203] has dealt with the puzzling question of the cause of infectious mononucleosis. According to him, there have been reports of unsuccessful attempts to prove the relation of various bacteria to the condition, but only one previous report has been made of the possible relation of a bacteria-free filtrate to the disease. According to van den Berghe and Liessens,[204] van den Berghe, Liessens and Kovacs [205] and van den Berghe and Liessens,[206] the agent is a virus, and this virus has been shown to produce the disease in monkeys. Furthermore, they state that freezing the virus appeared to increase its infectivity. The studies made by Nettleship may be summarized as follows: Sterile Berkefeld filtrates from nasal washings, as well as whole blood, from patients with the disease were inoculated into the chorioallantoic membranes of chick embryos; in a total of eight attempts to transmit the agent, positive results were obtained in 4; a continuation of the reaction through four to fourteen passages was obtained in about 50 per cent of the membranes, but the agent finally died out; unsuccessful attempts were made to transmit the virus to 25 mice by intraperitoneal inoculation; mononucleosis (prolymphocyte) could be produced in rabbits by the injection of a suspension of ground chick membranes, but it was not possible to obtain a positive heterophile reaction against sheep cells with the rabbit serum.

The clinical features of infectious mononucleosis are reviewed by McFarland,[207] who reiterates that the disorder is so common as to be almost endemic, yet one which is "seldom diagnosed" by many physicians and one associated with astonishing errors in diagnosis. The author has had to differentiate it from the following diseases: German measles, catarrhal jaundice, lymphatic leukemia, strangulated hernia and appendicitis. His chief reason for reviewing the characteristics of the disease is to emphasize the necessity of differentiating it from acute appendicitis. He raised the plausible possibility that the condition described as mesenteric lymphadenitis may not infrequently, or even always, be infectious mononucleosis. We must differ sharply with the author on one point; namely, his statement that "an occasional case runs a malignant and even fatal course." Patients with the disease may become severely ill, but in the event of a fatal termination considerable doubt is raised concerning the correctness of the diagnosis. In such cases the disease is usually some variety of leukemia, rather than infectious mononucleosis.

Ryan [208] stresses the fact that the protean nature of the clinical manifestations of infectious mononucleosis make the diagnosis uncertain unless a careful study

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203. Nettleship, A.: On Infectious Mononucleosis, Proc. Soc. Exper. Biol. & Med. **49**: 116, 1942.

204. van den Berghe, L., and Liessens, P.: Transmission de la mononucléose infectieuse humaine au Macacus rhesus: Résistance du virus aux basses températures, Compt. rend. Soc. de biol. **132**:90, 1939.

205. van den Berghe, L.; Liessens, P., and Kovacs, L.: Transmission de la mononucléose infectieuse humaine au Macacus rhesus: Culture du virus en tissu, Compt. rend. Soc. de biol. **131**:156, 1939.

206. van den Berghe, L., and Liessens, P.: Transmission de la mononucléose infectieuse humaine (fièvre ganglionnaire de Pfeiffer) au Macacus rhesus et passages successifs d'un virus filtrant, Compt. rend. Soc. de biol. **130**:279, 1939.

207. McFarland, J. E.: The Clinical Problem of Infectious Mononucleosis, J. Iowa M. Soc. **32**:10, 1942.

208. Ryan, J. M.: Infectious Mononucleosis, Minnesota Med. **25**:871, 1942.

is made of the blood and the atypical lymphocytes recognized, or unless the reaction against sheep cells is employed. A case is reported in which the disease constituted a diagnostic problem for the first two weeks of illness. During this time endocarditis, typhoid fever, undulant fever, acute cholecystitis and infectious mononucleosis were suspected. The cells characteristic of the disease did not appear until the eighth day of the illness, and the positive agglutination reaction was delayed until the twelfth day. The author warns that a negative reaction does not eliminate the diagnosis early in the course of the disease, and that one should keep in mind the fact that jaundice may be present.

Ash and Arbogast [209] report a series of 21 cases of infectious mononucleosis and review the literature in regard to this disorder. There was nothing unusual about their cases except that in 10 conjunctivitis was present, which caused them to stress the importance of this condition as a symptom. They emphasize that the appearance of a positive heterophile antibody reaction may be delayed. In 1 patient the reaction remained positive for a period of at least three months.

Some unusual manifestations of infectious mononucleosis are reported by Leavell and McNeel [210] in a series of 57 cases which they observed. They emphasize that commonly the clinical picture is so characteristic that the diagnosis is at once obvious but that atypical findings frequently occur and should be kept in mind when the observer is considering the diagnosis of this disease. Each of the 8 cases reported in detail had some unusual instructive feature, as follows: absence of all of the typical clinical features when the patient was first seen; a septic reaction with chills, fever and leukopenia; localized inguinal adenitis; a history of a tick bite, unexplained fever, a palpable spleen and agglutination of both sheep cells and Proteus X19, which suggested the diagnosis of Rocky Mountain spotted fever; symptoms which led to the removal of a normal appendix; fever, drowsiness, headache and changes in the spinal fluid which led to an erroneous diagnosis of encephalitis; jaundice.

Straus [211] emphasizes an important aspect of infectious mononucleosis which has not received the notice that it deserves, especially from surgeons. He reports the case of a patient who presented the signs and symptoms of acute appendicitis, for which she underwent appendectomy. The lesion in the lymphoid tissue of the appendix was found to be identical with the specific changes in the lymph glands in cases of infectious mononucleosis. These alterations, however, are not necessarily a constant finding, for in another case of infectious mononucleosis with the same complaints the appendix, by contrast, failed to reveal a similar lesion. In the case in which the appendix showed the characteristic lymphoid changes, the abdominal symptoms were considered to be greatly out of proportion to the degree of appendical involvement. The author concludes that no explanation is available for abdominal symptoms occurring in the course of infectious mononucleosis.

Sears [212] reports the interesting case of a 21 year old nurse who suffered from an attack of infectious mononucleosis of moderate severity. The only unusual aspect was a white blood cell count of 8,500 per cubic millimeter with 3 per cent polymorphonuclear neutrophils, 95 per cent lymphocytes and 1 per cent monocytes. This was noted on about the fifth day of the illness. There was also

209. Ash, H. H., and Arbogast, J. L.: Infectious Mononucleosis, J. Indiana M. A. **35**: 562, 1942.

210. Leavell, B. S., and McNeel, J. O.: Infectious Mononucleosis: Unusual Manifestations, Virginia M. Monthly **69**:180, 1942.

211. Straus, R.: Infectious Mononucleosis Simulating Acute Appendicitis with Description of a Specific Lesion of the Appendix, Am. J. Clin. Path. **12**:295, 1942.

212. Sears, W. G.: Glandular Fever with Granulocytopenia, Lancet **1**:703, 1942.

mild anemia with the color index somewhat below 1.0, as well as slight anisocytosis, poikilocytosis and polychromasia of the erythrocytes, which gradually improved. By about the twenty-fifth day of the illness the leukocyte count was 5,300 per cubic millimeter with 40 per cent neutrophils. This increase followed injection of pentnucleotide but, in our opinion, was not necessarily due to it. It is well known that commonly there is leukopenia with a decrease in the leukocytes and an increase in the lymphocytes in the first week of this disease. Rarely, however, does it reach the extent observed in this patient.

Carlile and Blackford [213] report an interesting case which was regarded as one of infectious mononucleosis but in which there was the most unusual complication of severe anemia. They recognize that anemia in this condition usually casts a serious doubt on the diagnosis and suggests the possibility that the patient may be suffering from a more serious condition, such as leukemia. Nevertheless, the diagnosis in this case was indicated by the high titer of the agglutination of sheep cells, namely, 1 : 2,048. At the time the test was positive, the blood findings were as follows: hemoglobin content, 59 per cent (7.8 Gm.); red blood cell count, 2,310,000 per cubic millimeter; leukocyte count, 7,800 per cubic millimeter; differential count, neutrophils 43 per cent, lymphocytes 56 per cent, eosinophils 1 per cent. The lymphocytes were reported to be of a type characteristic of infectious mononucleosis. Almost two years later the patient was reported as being in perfect health, although the blood was not examined at the time. It may be correct to state that this patient had infectious mononucleosis with the exceedingly rare complication of pronounced anemia, but it seems more probable that he had infectious mononucleosis with some other unrecognized cause for the anemia. There is a possibility the patient had acute lymphatic leukemia which went into remission and will eventually manifest itself again. In any event it is desirable that the authors record a complete follow-up note at some future date in order that the outcome of this important case may be recorded in the medical literature.

The case of a man aged 30 with the characteristic hematologic and clinical findings of infectious mononucleosis is presented by Magner and Brooks.[214] The atypical features which led to its being reported were hematuria, extensive presence of petechiae over the legs, with a few on the chest and buccal mucous membranes, an increased tendency to bleed from small cuts and oozing from the gums. Although the platelets were not counted, they are recorded as being greatly reduced at this time. The other blood findings were a hemoglobin percentage of 92 (Sahli), a red cell count of 4,950,000 per cubic millimeter and a leukocyte count of 18,800 per cubic millimeter with neutrophils 13 per cent, lymphocytes 77.5 per cent, monocytes 8.5 per cent and eosinophils 1 per cent. It was first thought that the patient had idiopathic thrombopenic purpura, but against this was the low percentage of neutrophils. The diagnosis of acute leukemia was unlikely because of the absence of anemia; furthermore, the lymphocytes, although of the type which may be found in leukemia, were much more suggestive of infectious mononucleosis. This observation led to a sheep cell agglutination test, and positive agglutination was found in the dilution 1 : 800. The patient, after being in the hospital for sixteen days, apparently recovered; examination two months after the onset showed the blood to be normal and agglutination positive only in the

213. Carlile, T., and Blackford, J. M.: Infectious Mononucleosis, with Anemia, Skin Rash and Jaundice, Northwest Med. **41**:137, 1942.

214. Magner, W., and Brooks, E. F.: Infectious Mononucleosis with Acute Thrombopenic Purpura, Bull. Acad. Med., Toronto **15**:189, 1942; Canad. M. A. J. **47**:35, 1942.

dilution 1 : 10. One questions the diagnosis in this case because hemorrhagic manifestations other than epistaxis are exceedingly rare in infectious mononucleosis, as is a reduction in the number of blood platelets. Such cases have been regarded previously as instances of purpura haemorrhagica with an atypical white cell response. It is also possible that the patient had infectious mononucleosis but with it had also thrombopenic purpura due to some drug, such as one of the sulfonamide compounds or allylisopropylacetylcarbamide (sedormid).

The case of a patient in whom infectious mononucleosis followed catheterization of the ureter for hydronephrosis is reported by Feil.[215] The ailment was characterized by fever, leukopenia with 60 per cent mononuclear cells, a cutaneous rash, abdominal pain, inguinal adenitis and jaundice. The Wassermann reaction was negative, but the heterophile antibody reaction was positive in the dilution 1 : 30. It was suggested that the infectious agent entered through the urinary tract as a result of the ureteral catheterization. The cutaneous rash was thought possibly to have resulted from the administration of phenobarbital. Furthermore, the author considers the possibility that this drug might have lowered the patient's resistance to such an extent that the infection became established. To use the basis for these speculative suggestions does not seem sound.

Seeds [216] discusses the importance of acute cervical adenitis in children and the differential diagnosis of this condition and emphasizes that infectious mononucleosis should always be considered when acutely enlarged glands are observed in a child.

A review of present knowledge of infectious mononucleosis is given by Spark.[217] Smeall [218] reviews the historical, clinical, laboratory and therapeutic aspects of infectious mononucleosis with special emphasis on the sheep cell agglutination test. A complete bibliography is appended. A brief résumé of the symptoms and the laboratory findings of infectious mononucleosis, together with a report of a case in which the chief clinical manifestation was fever, is given by White.[219]

Comment is made by Martin [220] on jaundice as a complication of infectious mononucleosis (glandular fever). He had previously reported 2 cases in which it occurred, and in this communication, adds 3 more. In each instance bile appeared in the urine, but cutaneous evidence was absent. The diagnosis in each case was confirmed by a positive Paul-Bunnell reaction (agglutination of sheep cells). He states that frank jaundice is uncommon in patients with infectious mononucleosis but that daily testing of the urine would probably more often reveal latent jaundice. Carter [221] reports a case of jaundice complicating infectious mononucleosis because of its comparative rarity. He cites Martin's statement that only 18 instances have been recorded. His case was that of a woman aged 28 who had all of the classic clinical evidences of the disease, including the hematic changes and positive agglutination of sheep cells in a dilution of 1 : 256. One week after the onset, jaundice appeared and remained for thirteen days. It was thought to be of the obstructive type. The fact that the jaundice deepened as the peripheral glands continued to enlarge was in accord with Martin's theory

215. Feil, L.: Ein Beitrag zur Frage des lymphämoiden Drüsenfiebers, Schweiz. med. Wchnschr. **71**:1071, 1941.
216. Seeds, A.: Acute Cervical Adenitis in Children, Texas State J. Med. **37**:592, 1942.
217. Spark, T. E. H.: Infectious Mononucleosis, M. J. Australia **2**:413, 1942.
218. Smeall, J. T.: Glandular Fever (Infectious Mononucleosis), Edinburgh M. J. **49**: 291, 1942.
219. White, J. R.: Infectious Mononucleosis: Case Report, U. S. Nav. M. Bull. **40**: 173, 1942.
220. Martin, L.: Glandular Fever with Jaundice, Lancet **1**:153, 1942.
221. Carter, A. B.: Glandular Fever with Jaundice, Lancet **1**:102, 1942.

that jaundice may result from enlargement of the glands in the portal fissure causing obstruction to the bile duct. Lymphatic leukemia and Weil's disease were considered in the differential diagnosis but eliminated by complete studies of the blood.

The case of a woman aged 20 with jaundice as a complication of infectious mononucleosis is reported by Gold.[222] On admission to the hospital she was regarded as having simple catarrhal jaundice, as she gave a history of nausea, vomiting and fever and was definitely icteric. If lymphadenopathy was present when the first examination was made, it was overlooked. The jaundice increased until the serum bilirubin amounted to 23.3 mg. per hundred cubic centimeters of blood, and the icterus index was 150 units. The van den Bergh reaction was strongly positive. The true nature of the illness was ultimately disclosed by the finding of the characteristic atypical lymphocytes in the circulating blood and by the agglutination of sheep cells in a dilution of 1 : 128. According to this author, a majority of observers consider that jaundice in this condition is due to associated hepatitis, but Tidy attributes it to enlargement of glands in the porta hepatis.

In an editorial comment in the *Lancet*[223] it is emphasized that infectious mononucleosis may simulate many diseases and that, as jaundice may occur, the diagnosis of catarrhal jaundice may be seriously entertained. The advice is given that the diagnosis of infectious mononucleosis should be considered in connection with any disease that appears to be catarrhal jaundice but that shows some unusual features, especially adenopathy or splenomegaly.

Bornstein[224] reports an instance in which human serum was observed to contain sheep cell antibodies in high titer (1 : 1,600) despite the fact that the patient suffered from neither serum sickness nor infectious mononucleosis. Such a reaction, fortunately for the differential diagnosis of infectious mononucleosis, is exceedingly uncommon, probably because it is ephemeral and also because the antibodies disappear quickly from serum specimens stored in the ice box. It is somewhat surprising that increased titers of heterophile antibodies are not observed more frequently, as it has been shown that an ever increasing number of bacteria contain heterophile antigen. Among such bacteria are the Shiga bacillus and several pneumococcus and Salmonella types. Occasionally positive reactions have been reported in cases of gonorrheal septicemia, aplastic anemia, scarlet fever, rubeola, tuberculosis and filariasis and after injections of liver extracts. Such positive reactions, however, must be exceedingly rare; that they do occur is evidence that there is some relation between heterophile antibodies in human serums and infections. In Bornstein's case, which gives support to this conception, a strain of Bacillus coli was cultured from the blood of a patient with severe cystitis. The patient's serum gave a positive heterophile antibody reaction (1 : 1,600); the antibodies concerned could be differentiated from the types observed in serum sickness and infectious mononucleosis and were of the Forssman variety. Unlike the antibodies in infectious mononucleosis, they disappeared rather quickly from the patient's blood, and the titer of serum kept in the ice box decreased rapidly. The Wassermann reaction was positive temporarily, although the Kahn and Kline reactions were negative. There was a transient increase in isoagglutinins. The antibodies in such cases are, according to the author, the same types as those encountered in normal serums, and this, according to him, makes it probable that there is a relation between the fluctuating titers of these antibodies and infections.

222. Gold, S.: Glandular Fever with Jaundice, Lancet **1**:103, 1942.
223. Annotations, Lancet **1**:112, 1942.
224. Bornstein, S.: Heterophile Antibody Reaction Caused by Bacterial Infection, Ann. Int. Med. **16**:472, 1942.

Straus and Bernstein [225] have made an investigation of the five different technics for the demonstration of the sheep cell agglutinins in the blood serum of patients with infectious mononucleosis. According to them, each of the following factors has an important effect on the sensitivity of the test: the amount of blood serum employed; the serial dilution of the serum; the concentration of the sheep cell suspension added to the serum; the temperature at which the mixtures are maintained. After a careful serologic study of a large number of patients with and without infectious mononucleosis, they conclude that series determinations are of more diagnostic value than single determinations and that the "single tube test," introduced by Straus in 1936, is of diagnostic value when positive but does not exclude the disease when negative. They state that increased titers of heterophile agglutinins had been reported for the blood serums of patients with serum sickness, pneumonia, scarlet fever, measles, tuberculosis, filariasis and aplastic anemia and for those of patients treated with quinine or parenteral liver extract. In the authors' limited experience they have been unable to confirm these claims, although the agglutination titers were high in a case of serum sickness. They consider that the differential absorption test is of diagnostic value, especially in cases of infectious mononucleosis, cases in which borderline titers of heterophile agglutinins are met with, and cases with a history of injections of horse serum.

Lonergan [226] reviews the development of present knowledge of the heterophile antibody reaction in infectious mononucleosis and discusses the Straus modification of the Paul-Bunnell test. It was concluded that a case cannot be classed as one of infectious mononucleosis on the simple or presumptive Paul-Bunnell test alone. By carrying out absorption tests on all serums yielding titers of 1:50 or higher with the presumptive test, the agglutinins may be correctly classified as agglutinins of serum sickness, of "normal" type or of infectious mononucleosis.

Canzani, Varela Fuentes and di Bello [227] discuss the serologic diagnosis of infectious mononucleosis and review present knowledge of the heterophile antibody test for the disease. As the disorder has varied clinical manifestations, this test is of value from a diagnostic standpoint. They warn that in some cases of infectious mononucleosis there may be a transient false positive serologic reaction for syphilis. They discuss the disease from the standpoint of etiology and consider the relationship of Listerella monocytogenes to the condition. In their opinion, the significance of this organism as a causative agent has not been demonstrated.

It is emphasized by Berkley [228] that as yet no successful treatment has been devised for infectious mononucleosis, despite the fact that in patients other than infants it constitutes a great handicap and makes for marked economic loss of time. The author treated 4 patients by intravenous injection of 100 cc. of scarlet fever convalescent serum and observed complete clinical recovery in each within forty-eight hours. He states that these results bring up the following questions: Is the benefit due to a nonspecific action of human serum? If this is true, similar effects should be produced by pooled normal human serum. Is it possible that

225. Straus, R., and Bernstein, M. T.: Further Serological Studies in Infectious Mononucleosis, Am. J. Clin. Path. **12**:174, 1942.

226. Lonergan, M.: Straus Technique of the Paul-Bunnell Test, Canad. M. J. Technol. **4**:107, 1942.

227. Canzani, R.; Varela Fuentes, B., and di Bello, R.: Reacciones serológicos de sifilis "falsas positivas" de la mononucleosis infecciosa (fiebre ganglionar de Pfeiffer), Semana méd. **2**:502, 1941.

228. Berkley, H. K.: Infectious Mononucleosis: Its Treatment with Scarlet Fever Convalescent Serum, J. Pediat. **20**:26, 1942.

infectious mononucleosis is due to a member of the streptococcic group closely allied to the streptococcus of scarlet fever? Is 100 cc. the correct dosage?

Smyth [229] reports the case of a young man with a severe attack of infectious mononucleosis who made a prompt recovery after receiving on four successive days 20 cc. of serum from a patient convalescing from this disease. On the fourth and sixth hospital days 100 roentgens was applied locally to his throat. The only unusual finding in the case was a serum agglutination of typhoid bacilli in a dilution of 1:640, which the author concluded was due either to cross agglutination or to nonspecific stimulation of his typhoid antibodies. He had received typhoid vaccine three years previously. The agglutination of sheep cells occurred in a dilution of 1:356. It is difficult to evaluate the effects of treatment, and the final conclusion regarding the true efficacy of convalescent serum in this condition must await many more trials.

The effect of the administration of sulfathiazole in 7 patients with infectious mononucleosis was studied by Hoffman, Lees and Comroe.[230] It had been their experience that the usual measures employed in the treatment of this condition were disappointing and that the patients usually faced a long period of disability following the subsidence of the acute phase of the illness. A total dose of from 15 to 23 Gm. was given to each patient over a period of six to ten days. The authors' limited experience did not warrant definite evaluation of this form of therapy, but the results attained appeared to be superior to those with other forms of treatment, since the fever, malaise, sore throat and much of the adenopathy disappeared after four to five days. The drug did not produce any appreciable change in the blood picture.

In a study of 29 patients with the disease whose serum gave agglutination of sheep cells, the highest white blood cell count was 26,400 and the lowest 3,700 per cubic millimeter; the only constant finding in the blood was definite lymphocytosis at some time during the disease. The clinical picture did not vary from that commonly observed; i. e., fever was present in 80.7 per cent, sore throat in 72.4 per cent, and general malaise in 72.4 per cent. Cervical adenopathy was noted in 100 per cent of the patients. The authors did not observe evidence of a person to person spread in any instance, nor did they have more than 1 case from the same fraternity house or dormitory at any one time. In conclusion it is stated that sulfathiazole produced prompt clinical improvement in the 7 cases in which it was used, without marked change in the white blood cell count or in the differential formula.

LYMPHOMATOID DISEASES, LEUKEMIA AND RELATED DISORDERS

Hodgkin's Disease.—A series of 265 cases of Hodgkin's disease studied in the Memorial Hospital for the Study of Cancer and Allied Diseases, New York, has been analyzed by Slaughter and Craver.[231] The average survival time of the patients following the initial therapy was found to be thirty-three and eight-tenths months, and the average age of onset was 35 years. A predilection of the disease for males was observed in this study, and painless enlargement of the cervical lymph nodes was the commonest presenting symptom. Two regimens of roentgen therapy have been used in this clinic. The first, or "palliative," one

229. Smyth, L. A.: Report of Case of Infectious Mononucleosis, Cincinnati J. Med. **23**: 292, 1942.

230. Hoffman, H. T.; Lees, H. D., and Comroe, B. I.: Use of Sulfathiazole in Infectious Mononucleosis, Am. J. M. Sc. **203**:731, 1942.

231. Slaughter, D. P., and Craver, L. F.: Hodgkin's Disease: Five Year Survival Rate; Value of Early Surgical Treatment; Notes on Four Cases of Long Duration, Am. J. Roentgenol. **47**:596, 1942.

consists of moderate doses of roentgen radiation, sufficient to control symptoms, whereas the second or "obliterative" one aims at radical destruction of the disease cells wherever these are well localized. Five patients who had localized enlargement of lymph nodes were treated surgically, and excellent results were obtained in 3 of them. Although this group is too small to permit far reaching conclusions, the authors suggest that surgical procedures may prove of value in those patients in whom the disease is limited to a single chain of lymph nodes.

Haden and Burns [232] point out that, unlike lymphosarcoma and leukemia, Hodgkin's disease has never been reported in lower animals. Of their 47 patients, 10 complained initially of general symptoms, such as weakness, fever, loss of weight, anorexia and dyspnea, and the remaining 37 patients first noted lymphadenopathy, most commonly cervical. Splenomegaly occurred in 17 patients and hepatomegaly in 6. In 39 patients hypochromic anemia developed during the course of their illness. The total leukocyte count showed wide variation, but in general neutrophilia and relative lymphopenia and monocytopenia occurred whenever there was marked leukocytosis. The sexes were affected nearly equally, and the average age of incidence was 35 years. In this series the average duration of the disease was two and a half years.

In their survey of the osseous lesions of Hodgkin's disease, Vieta, Friedell and Craver [233] found at necropsy evidence of involvement of bones in 49 per cent of their 47 cases. In 257 cases the incidence of skeletal lesions demonstrable by roentgen examination was 14.8 per cent. Hodgkin's disease as contrasted with lymphosarcoma does not often include destruction of cortical bone. The pelvis, the vertebrae, the ribs and the femurs are most frequently attacked, with production of pain and local tenderness. A mixed osteoblastic and osteolytic lesion is characteristically found on roentgen examination, and the blood phosphatase level is elevated whenever osteoblastic reactions occur. The life expectancy in Hodgkin's disease has not been lessened by the presence of osseous lesions, according to these authors. The use of radiation has effected temporary improvement in many of their cases.

Zakon and Falkenstein [234] report their biopsy and necropsy observations in a case of mycosis fungoides. They believe that mycosis fungoides is a disease *sui generis* and can be differentiated from Hodgkin's disease by morphologic differences in the multinucleated giant cells (not clearly explained in this article) and by the absence of fibrosis in the lesions of mycosis fungoides. The infrequency of visceral lesions in mycosis fungoides and the dissimilarity of the dermal manifestations of the two diseases are substantiating arguments, these authors believe.

Wise [235] believes that by employing the Wintrobe method of determining the erythrocyte sedimentation rate valuable information regarding the activity of Hodgkin's disease can be gained. In 6 cases the rate was elevated whenever there was clinical evidence of progression. In 2 cases the rate was slowed just before death. In explanation the author refers to Wintrobe's statement that the erythrocytes of cachectic tuberculous patients may have a normal rate. He also suggests that inasmuch as these patients are severely anemic, the apparently low rate may be due to inaccuracy of the sedimentation correction factor.

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232. Haden, R. L., and Burns, J. T.: Hodgkin's Disease: Review of Forty-Seven Cases, Cleveland Clin. Quart. **9**:144, 1942.

233. Vieta, J. O.; Friedell, H. L., and Craver, L. F.: A Survey of Hodgkin's Disease and Lymphosarcoma in Bone, Radiology **39**:1, 1942.

234. Zakon, S. J., and Falkenstein, A. P.: Mycosis Fungoides: Report of a Case with Autopsy Findings, Illinois M. J. **82**:224, 1942.

235. Wise, B.: The Sedimentation Rate in Hodgkin's Disease, J. Lab. & Clin. Med. **27**: 1200, 1942.

Specific cutaneous lesions appeared initially in the case of Reimann, Havens and Herbut.[236] There was absence of superficial lymphadenopathy, although at necropsy enlarged abdominal nodes were found, which were histopathologically diagnostic of Hodgkin's disease. A nodular, ulcerated lesion of the rectum producing obstructive symptoms in a man 33 years of age was proved to be Hodgkin's granuloma, according to Spiesman and Rubenstein.[237]

Klawans [238] has reported the onset of Hodgkin's disease during the sixth month of pregnancy. The disease ran a rapid course in the 33 year old primigravida, and she died forty-five days after delivery. Parade [239] states that in his case of pregnancy complicated by Hodgkin's disease the child died shortly after delivery. No pathologic changes suggestive of Hodgkin's disease were found at necropsy. In his search of the medical literature he was able to discover no evidence pointing to transplacental transfer of the disease. Schwind and Hyde [240] report their findings in a 4 month old girl whose peripheral blood contained immature cells resembling lymphoblasts. The diagnosis of Hodgkin's disease was established on biopsy of a cervical lymph node. Bernreiter [241] found agglutination of the brucellas of undulant fever in the case of a male patient afflicted with Hodgkin's disease, although no further evidence of active infection with brucellas was obtained. The author wonders if brucellosis may produce a lesion resembling Hodgkin's disease.

Lymphosarcoma.—In an excellent discussion of the malignant types of lymphoma Gall and Mallory [242] recognize seven distinct types: (1) stem cell lymphoma, (2) clasmatocytic lymphoma, (3) lymphoblastic lymphoma, (4) lymphocytic lymphoma, (5) the lymphoma of Hodgkin's disease, (6) the sarcoma of Hodgkin's disease and (7) follicular lymphoma. The first four types possess a simple cytologic structure in contrast with the complex form of the remaining three types. From the analysis of their 618 cases the authors have found the onset of lymphoma to occur most frequently between the ages of 37 and 51 years. The lymphoma of Hodgkin's disease, lymphoblastic lymphoma and lymphocytic lymphoma occur with significant frequency in the first three decades of life whereas the clasmatocytic and follicular types afflict primarily the aged. Enlargement of the peripheral lymph nodes was found in 90 per cent of the entire series, while splenomegaly occurred most frequently with the lymphocytic type and least often with the sarcoma of Hodgkin's disease, stem cell lymphoma and clasmatocytic lymphoma. The highest incidence of osseous lesions was noted with the clasmatocytic type. Hematologic studies frequently demonstrated anemia of varying degree throughout the entire series of cases. Thrombocytosis was a common accompaniment of Hodgkin's sarcoma, and thrombopenia of lymphoblastic and lymphocytic lymphoma. The lymphocytic and the lymphoblastic lymphoma and the sarcoma of Hodgkin's disease often produce leukocytosis. Two

236. Reimann, H. A.; Havens, W. P., and Herbut, P. A.: Hodgkin's Disease with Specific Lesions Appearing First in the Skin, Arch. Int. Med. **70**:434 (Sept.) 1942.

237. Spiesman, M. G., and Rubenstein, H. I.: Hodgkin's Lymphogranuloma (Rectal Stricture): Report of a Case, Ann. Int. Med. **17**:349, 1942.

238. Klawans, A. H.: Pregnancy Complicated by Hodgkin's Disease, Am. J. Obst. & Gynec. **43**:895, 1942.

239. von Parade, G. W.: Diaplazentare Übertragung der Lymphogranulomatose? Deutsche med. Wchnschr. **68**:862, 1942.

240. Schwind, J. L., and Hyde, G. M.: Hodgkin's Disease in an Infant: Report of a Case with a Peculiar Peripheral Blood Picture, J. Pediat. **21**:238, 1942.

241. Bernreiter, M.: Hodgkin's Disease Complicated by Brucellosis, J. Kansas M. Soc. **43**:330, 1942.

242. Gall, E. A., and Mallory, T. B.: Malignant Lymphoma: A Clinico-Pathological Survey of Six Hundred and Eighteen Cases, Am. J. Path. **18**:381, 1942.

years was the average duration of life for the entire series. The authors believe that judicious use of radiation as well as surgical treatment in certain selected cases may prolong life.

Stout [243] has studied 218 patients with lymphosarcoma, 156 of whom received roentgen therapy, surgical treatment or a combination of both. Of the treated patients, 21.8 per cent survived for five years and 14.8 per cent were symptom free at the end of this period of time. Only 3.2 per cent of the untreated patients lived for a similar length of time, and all of them had experienced recurrence of the tumor growth. It was observed that prolonged periods of survival were not obtained for patients afflicted with lymphosarcoma during the first three decades of life. Of the types of lymphosarcoma included in the series, the reticulum cell was found to be the most rapidly destructive. That favorable therapeutic results are attained only while the tumor remains localized is emphasized by this author. Jenkinson, Kinzer and Brown [244] are in agreement with Stout regarding the greater invasiveness of the reticulum cell sarcoma. Whereas their patients with lymphocytic sarcoma lived an average of forty-eight months after the onset of symptoms, the patients afflicted with reticulum cell sarcoma lived only twenty-four months.

Vieta, Friedell and Craver [233] discovered osseous lesions in 29 per cent of the cases of lymphosarcoma in which autopsy was done, and destruction of cortical bone frequently. These lesions, which were purely osteolytic, were widely disseminated over the entire skeleton and developed late in the course of the disease. Temporary improvement, amounting at times to complete regeneration of the bone, was observed after roentgen therapy.

Thirty-seven cases of tonsillar lymphosarcoma in which treatment was given at the Radium Institute of Paris, France, are reported by del Regato.[245] The earliest symptoms may be obstructive, inflammatory or metastatic. Following irradiation of the cancers, the details of which are included in the article, 40.5 per cent of the patients have survived from six to fourteen years without symptoms or signs of recurrence. Eight treated patients later had metastatic lesions of the cervical lymph nodes, whereas only a single patient had recurrence in the tonsillar area.

Two types of dermal reaction in lymphoblastoma cutis are recognized by Senear.[246] The first has the specific histologic pattern of the primary disease, and the second is a toxic manifestation of nonspecific character.

Interesting reports have been contributed to the literature by several investigators. Hine [247] presents his study of a 58 year old woman in whom a lymphomatous tumor of the left orbit developed. A lymphosarcoma of the lacrimal gland apparently cured by surgical removal and irradiation of the site is described by Perera.[248] Tenenbaum [249] was able to discover in the medical literature only 5 authenticated cases of lymphosarcoma of the prostate, to which he adds a report

243. Stout, A. P.: Is Lymphosarcoma Curable? J. A. M. A. **118**:968 (March 21) 1942.

244. Jenkinson, E. L.; Kinzer, R. E., and Brown, W. H.: Lymphosarcoma, with Special Reference to the Reticulum-Cell Type, Am. J. Roentgenol. **48**:433, 1942.

245. del Regato, J.: Roentgentherapy of Lymphosarcomas of the Tonsil, Radiation Therapy, Tumor Inst., Seattle, 1941, no. 2, p. 67.

246. Senear, F. E.: Lymphoblastoma Cutis, M. Clin. North America **26**:1, 1942.

247. Hine, M. L.: Report on a Case of Lymphoma of the Orbit, Brit. J. Ophth. **26**:297, 1942.

248. Perera, C. A.: Lymphosarcoma of the Lacrimal Gland: Report of a Case with Giant Lymph Follicle Hyperplasia, Arch. Ophth. **28**:522 (Sept.) 1942.

249. Tenenbaum, J.: Lymphosarcoma of Prostate and Epididymis: Case Report, J. Urol. **48**:113, 1942.

of a case. The lesion is interesting inasmuch as some pathologists believe no lymph tissue exists in the prostate. However, rudimentary lymph nodes have been described in prostatic tissue, and it is in all probability from one of these sites that the lymphosarcoma arose. The presence of generalized lymphosarcomatosis in a patient who had congenital absence of the spleen is reported by Charache.[250] Giant follicular lymphoblastoma of multicentric origin has been described by Held and Chasnoff.[251] Involvement of both the spleen and the lymph nodes was noted in their case. Jahsman [252] reports satisfactory remissions following roentgen therapy in a 53 year old man who had widespread follicular lymphoblastoma.

Leukemia.—Although no disease has proved more baffling and more discouraging to the clinician and the investigator than leukemia, there is no discernible slackening of interest in it. In fact, the new investigational and therapeutic opportunities offered by the use of radioactive elements have acted as a powerful stimulus to workers in this field. Recent studies concerning radioactive phosphorus will be discussed in a separate section.

A statistical analysis of 64 cases of chronic myelogenous leukemia and 64 cases of chronic lymphocytic leukemia has been contributed by Pascucci.[253] The average age of onset of chronic myelogenous leukemia was 41.1 years, and that of chronic lymphocytic leukemia, 49.6 years. Males predominated slightly in the group suffering from chronic lymphocytic dyscrasia whereas an equal distribution with respect to sex was found in the group with myelogenous leukemia. Almost half (44 per cent) of the patients suffering from myelogenous leukemia complained initially of symptoms related to splenomegaly, in contrast with those who had lymphatic leukemia, 63 per cent of whom noted progressive enlargement of peripheral lymph nodes at the onset and only 27 per cent of whom complained of symptoms related to enlargement of the spleen. The average duration of life was two and five-tenths years in the group with myelogenous leukemia and two and eight-tenths years in the group with lymphocytic dyscrasia. The author concludes that initial splenomegaly occurs in lymphocytic leukemia and early lymphadenopathy in myelogenous leukemia more frequently than was formerly supposed.

In an analysis of 1,500 cases of leukemia in children Cooke [254] found the highest incidence in children of 3 and 4 years. A sharp decline occurred during the following three years, followed thereafter by a more gradual decrease throughout later childhood. Forty per cent of all the patients were between 3 and 5 years of age. Approximately 60 per cent of the patients were boys. The appearance of a peak of incidence during the third and fourth year is in contrast with statistics of other tumors of childhood, most of which appear with increasing frequency during later childhood. On the other hand, the age incidence of childhood leukemia and that of childhood infections parallel each other closely. For this reason and for the reason that leukemia often develops shortly after an acute infection, the author believes that such infections are one of the important factors in the production of these forms of blood dyscrasia in children.

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250. Charache, H.: Lymphosarcomatosis and Congenital Absence of Spleen, New York State J. Med. **42**:1363, 1942.

251. Held, I. W., and Chasnoff, J.: Giant Follicular Lymphoblastoma (Giant Lymph Follicle Hyperplasia), Am. J. M. Sc. **204**:232, 1942.

252. Jahsman, W. E.: Follicular Lymphoblastoma, J. A. M. A. **120**:1126 (Dec. 5) 1942.

253. Pascucci, L. M.: Chronic Leukemia: A Statistical Study of Symptoms, Duration of Life, and Prognosis, Radiology **39**:75, 1942.

254. Cooke, J. V.: The Incidence of Acute Leukemia in Children, J. A. M. A. **119**:547 (June 13) 1942.

Four hundred and ninety-five cases of leukemia have been reviewed by Bethell [255] and have been classified into three main groups, the lymphogenous, the myelogenous and the histogenous, according to the type of parent cell involved. Lymphogenous leukemia has been further subdivided into the lymphocytic, lymphosarcoma cell and lymphoblastic types; myelogenous leukemia, into myeloblastic, myelocytic and myelomonocytic (Naegeli) types, and histogenous leukemia, into the histiomonocytic (Schilling) form. Of the types of acute leukemia, the lymphoblastic predominates during the first two decades, whereupon, after the age of 20, the myeloblastic gains ascendency. The commonest type of chronic leukemia during the first six decades is the myelocytic type. After the age of 60 the lymphocytic type occurs with relatively increasing frequency. Acute monocytic leukemia was observed most commonly during the fourth and fifth decades, and chronic monocytic leukemia between the ages of 30 and 60 years without special predilection for any age group. Bethell believes that the incidence of acute leukemia may be actually increasing.

In a more detailed study of the lymphogenous (lymphatic) group, 190 cases were reviewed by the same author.[256] This group of cases comprised 43.8 per cent of all cases of leukemia studied at the Simpson Memorial Institute over a thirteen year period. There were 52 cases of lymphoblastic leukemia, 68 cases of lymphocytic leukemia and 70 cases of lymphosarcoma cell leukemia. The author considers the lymphoblastic dyscrasia as a "cataclysmic disaster of childhood," occurring most frequently in the first decade of life, predominantly in boys. The presenting symptoms were commonly those attendant on rapidly developing anemia, and the average life expectancy was only four months. Radiation therapy proved to be uniformly unsuccessful in these cases. Lymphocytic leukemia occurred under the age of 40 years in only 1 case, whereas lymphosarcoma cell leukemia showed no predilection with respect to age among females, although before the age of 10 years and after the age of 40 years it predominated in males. The most common initial sign of the lymphocytic and the lymphosarcoma cell leukemia was enlargement of the peripheral lymph nodes. The average duration of life of patients with lymphosarcoma cell leukemia was found to be one year in this series, in contrast with the four and nine-tenths years of the group of patients with lymphatic leukemia. Following irradiation of the lesions, a satisfactory, although temporary, remission of symptoms was the rule in the cases of lymphocytic leukemia, in contrast with the cases of lymphosarcoma cell leukemia, in which the results of roentgen therapy were generally less gratifying.

In their series of 22 cases of aleukemic paramyeloblastic leukemia, Evensen and Schartum-Hansen [257] found the duration of the disease to vary from two to fifteen months, with a more rapid course in younger patients. The ages of the patients ranged from 2½ to 71 years. Progressive normocytic or macrocytic anemia, thrombopenia and an elevated erythrocyte sedimentation rate were constant laboratory findings. The authors emphasize their findings of joint and skeletal pain. Splenomegaly was discovered during the course of the disease in 9 patients, whereas hepatomegaly occurred in 12 patients and lymphadenopathy in 9. Stomatitis was a late complication in 6.

255. Bethell, F. H.: Leukemia: A Survey of Cases Observed Over a Fifteen Year Period, Univ. Hosp. Bull., Ann Arbor **8**:65, 1942.

256. Bethell, F. H.: Lymphogenous (Lymphatic) Leukemia: Diagnostic, Prognostic and Therapeutic Considerations Based on an Analysis of Its Morphologic and Clinical Variants, J. A. M. A. **118**:95 (Jan. 10) 1942.

257. Evensen, O. K., and Schartum-Hansen, H.: The Symptomatology of Aleukemic Paramyeloblastic Leukemia, Acta med. Scandinav. **107**:227, 1941.

That the first signs and symptoms of leukemia may be of ocular origin is emphasized by Hansen,[258] who presents a detailed discussion of the ophthalmologic changes in leukemia. Unfortunately, he presents no statistics concerning the relative frequency of the various abnormalities described.

A general review of monocytic leukemia has been contributed by Evans,[259] which is too lengthy to permit detailed discussion.

Dental journals have contained several interesting case reports in which the oral lesions of patients with leukemia have been discussed. According to Pasternack, Abbott and Werner,[260] the presenting symptoms and signs may be (1) simple toothache, (2) swelling or hypertrophy of gingivae, (3) necrosis and ulceration of gingivae, (4) osteomyelitis of the jaw and (5) hemorrhages from the gingivae. A case of acute lymphatic leukemia is presented in which toothache was the earliest symptom of the blood dyscrasia. Armbrecht and Apple[261] report the case of a 32 year old man who had spongy, swollen gums, which bled excessively. The hematologic findings were compatible with a diagnosis of lymphatic leukemia (probably acute, although not so stated). Mason[262] reports a case of chronic myelogenous leukemia in which severe gingival hypertrophy was a prominent feature. Similar findings in a patient suffering from acute monocytic leukemia were noted by Saghirian and Jones.[263] Mallett and Guralnick[264] point out the similarity of leukemic gingivitis and gingival hypertrophy caused by dilantin sodium (phenytoin sodium; sodium diphenyl hydantoin).

Hartz and van der Sar,[265] in their report on a patient who died of chloroleukemia, emphasize the unusually marked invasiveness of this variant of myelogenous leukemia. Pathologic examination demonstrated widespread invasion and destruction of the walls of blood vessels, formation of tumor thrombi and destruction of bronchial walls, as well as parenchymal infiltration of the kidneys and the pancreas. M'Glone's[266] patient, a 10 year old boy, presented bilateral orbital chloroma, which the author believes originally developed in the sphenoid sinuses. At autopsy green urine was found in the bladder. No detailed studies were made, however, to establish the nature of the urinary pigment.

That specific cutaneous lesions rarely occur in myelogenous leukemia is apparent in the study of Paul and Limarzi,[267] who were able to glean only 20 cases from the medical literature. They report a case in which indurated red nodules of the skin developed and in which improvement followed radiation therapy. Biopsy at a time when the peripheral blood was indicative of chronic myelogenous leukemia showed diffuse infiltration of the corium and subcutaneous tissues with masses of blast cells and occasional myelocytes. Shortly thereafter

258. Hansen, E. W.: Eye Lesions in Leukemia, Minnesota Med. **25**:580, 1942.

259. Evans, T. S.: Monocytic Leukemia: General Review of the Subject, Medicine **21**: 42, 1942.

260. Pasternack, J. G.; Abbott, G. A., and Werner, R. D.: Leukemia Gingivopathy: A Case of Acute Lymphatic Aleukemic Leukemia, J. Am. Dent. A. **29**:1193, 1942.

261. Armbrecht, E. C., and Apple, C. A.: Lymphatic Leucemia, Am. J. Orthodontics **28**: 607, 1942.

262. Mason, H.: Gingival Hypertrophy Due to Myelogenous Leucemia, Am. J. Orthodontics **28**:738, 1942.

263. Saghirian, L. M., and Jones, C. A.: Acute Monocytic Leucemia: A Case Report, Am. J. Orthodontics **28**:561, 1942.

264. Mallett, S. P., and Guralnick, W. C.: A Case of Acute Monocytic Leucemia, Am. J. Orthodontics **28**:95, 1942.

265. Hartz, P. H., and van der Sar, A.: Chloroleukemia: Report of a Case with Special Reference to Its Neoplastic Nature, Am. J. Path. **18**:715, 1942.

266. M'Glone, J. A.: A Case of Chloroma, Glasgow M. J. **138**:47, 1942.

267. Paul, J. T., and Limarzi, L. R.: Specific Cutaneous Lesions in Chronic Myeloid Leukemia: Clinical Significance, Arch. Dermat. & Syph. **45**:897 (May) 1942.

the leukemia entered an acute phase, in which numerous myeloblasts were found in the blood, and the patient soon died. Inasmuch as myeloblasts were found in the skin in large numbers at a time when the leukemic process was of a chronic type and the blood was practically devoid of these early cells, the authors suggest that there might well have been primary autochthonous cutaneous derivation of the myeloblasts from local reticuloendothelial elements rather than metastatic deposition of these immature cells in the dermis.

Chronic myelogenous leukemia occurring in a 6 week old boy has been reported by Poncher, Weir and Limarzi.[268] They believe this to be the youngest patient with the disease on record. Goehl [269] presents the clinical and hematologic findings in frank eosinophilic leukemia occurring in a lad of 18 years. Although the familial occurrence of leukemia is not common, Hornbaker [270] has been able to present a detailed account of 3 sisters with the disease. Two of them had lymphatic leukemia, and the third, myelogenous leukemia. All were middle aged. Four other siblings had no evidence of any blood dyscrasia, and there was no familial history of leukemia in preceding generations.

Farber and Bylebyl [271] point out that chronic lymphatic leukemia is rarely complicated by puimonary tuberculosis, whereas the association of myelogenous leukemia and tuberculosis is not unusual. Three cases in which chronic lymphatic leukemia and active pulmonary tuberculosis occurred concomitantly are presented. An 83 year old patient of Richards and Moench [272] has been observed at intervals during the past sixteen years and has shown on each occasion hematologic abnormalities compatible with a diagnosis of chronic lymphatic leukemia. In a short article Sterne [273] describes and illustrates with photomicrographs the evolution of the monocyte. Brief reports of 5 cases of monocytic leukemia are included.

An antileukocytic sheep serum has been prepared by Thiersch, [274] who injected human myelogenous leukemic cells into these animals. The serum of the immunized sheep caused a strong febrile reaction six hours after its injection into patients with myelogenous leukemia. Both of these patients had previously had several courses of roentgen therapy and their leukemia had become refractory to this type of treatment. Forty days after the injection of the antileukocytic serum, further radiation was given, and a temporary clinical improvement followed.

Heinle, Wearn and co-workers [275] report a group of interesting experiments in which repeated injection of extracts from the urine of patients who had myelogenous leukemia into the tissues of young male guinea pigs produced myeloid hyperplasia and metaplasia. Soon anemia developed, followed by a marked increase in the leukocyte count. Concomitant with the leukocytosis, immature myelocytes and myeloblasts appeared in the peripheral blood. The animals appeared clinically

268. Poncher, H. G.; Weir, H. F., and Limarzi, L. R.: Chronic Myelogenous Leucemia in Early Infancy: A Case Report, J. Pediat. **21**:73, 1942.

269. Goehl, R. O.: Eosinophilic Leukemia, with Case Report, Journal-Lancet **62**:252, 1942.

270. Hornbaker, J. H.: Chronic Leukemia in Three Sisters, Am. J. M. Sc. **203**:322, 1942.

271. Farber, J. E., and Bylebyl, H.: Lymphatic Leukemia and Tuberculosis, Am. J. Clin. Path. **12**:253, 1942.

272. Richards, G. G., and Moench, L. G.: Chronic Lymphatic Leukemia: Report of a Case with Survival for Sixteen Years, J. A. M. A. **119**:632 (June 20) 1942.

273. Sterne, E. H., Jr.: Diagnosis of Monocytic Leukemia from an Examination of the Peripheral Blood Stained with Wright's, with a Report of Five Cases, Ohio State M. J. **38**:234, 1942.

274. Thiersch, J. B.: Antileucocytic Sheep Serum as Sensitizing Agent in Chronic Myeloid Leuchaémia Refractory to Deep X-Ray Therapy, M. J. Australia **1**:225, 1942.

275. Heinle, R. W., and others: Myeloid Hyperplasia and Metaplasia Induced by Extracts of Urine from Patients with Myelogenous Leukemia, Ann. Int. Med. **17**:902, 1942.

ill and lost weight. Necropsy demonstrated myeloid hyperplasia in the bone marrow and myeloid metaplasia in the spleen, the liver and the adrenal glands of the experimental animals. No definite tissue response was observed in guinea pigs given injections of extracts prepared from the urine of patients with lymphatic leukemia. Details of the methods of extraction are presented. The authors believe that in the urine of patients who have chronic myelogenous leukemia there occurs an unknown substance capable of producing myeloid hyperplasia and metaplasia when injected into normal guinea pigs. Miller [276] demonstrates lowered resistance to infection in guinea pigs similarly treated. Small doses of an avirulent strain of staphylococci injected into guinea pigs previously treated with the extracts from the urine of leukemic patients caused a high mortality, whereas considerably larger doses of the same strain of staphylococci produced no reaction when injected into control animals.

In their extended metabolic studies of spontaneous and induced leukemia of mice, Burk and co-workers [277] found no increase of anaerobic glycolysis in the lymph nodes with the induced leukemia. This finding contrasted with the results of previous experiments conducted on lymph nodes of spontaneously leukemic mice. On the other hand, the anaerobic glycolysis of leukemic mouse liver was considerably increased above the rate of control liver, and the leukemic liver tissue produced lactic acid whereas normal liver tissue consumed this metabolite. In the Rf strain of mice the aerobic glycolysis of leukemic lymph nodes exceeded that of control tissue by as much as 50 to 100 per cent. Hall and Furth [278] found no difference in the oxygen consumption of leukemic and normal mouse lymph nodes. An inconstant increase of aerobic glycolysis was observed in leukemic lymph nodes, whereas anaerobic glycolysis was increased invariably.

Interspecies embryonic transmission of avian leukosis was successfully performed by Pollard and Hall,[279] who employed the agent of fowl leukosis. Leukosis occurred in duck, turkey, guinea fowl, pheasant and quail embryos. That bone marrow of normal fowls becomes infective after explantation and in vitro cultivation in contact with leukotic plasma has been demonstrated in the experiments of Doljanski and Pikovski.[280] They reported that the agent of fowl leukosis requires the presence of living cells in order to maintain its activity.

Kirschbaum and Strong [281] believe that the efficiency of methylcholanthrene, 3,4-benzpyrene and 1, 2, 5, 6-dibenzanthracene in hastening the appearance of leukemia in the high leukemia F strain of mice bears a direct relation to the potency of these carcinogens in inducing other types of mouse tumors. The experiments of McEndy, Boon and Furth [282] have demonstrated that roentgen exposure may act as a synergistic agent and increase slightly the incidence of

276. Miller, F. R.: The Influence of Secondary Factors on Induced Leukemia, J. Clin. Investigation **21**:643, 1942.

277. Burk, D., and others: Metabolism of Induced and Spontaneous Leukemia in Mice, J. Nat. Cancer Inst. **3**:249, 1942.

278. Hall, V. E., and Furth, J.: Metabolic Studies in Mouse Leukemia: The Metabolism of Lymph Nodes in Lymphoid Leukemia, Cancer Research **2**:411, 1942.

279. Pollard, M., and Hall, W. J.: Interspecies Transmission of Avian Leucosis in Embryos, Am. J. Vet. Research **3**:247, 1942.

280. Doljanski, L., and Pikovski, M.: Agent of Fowl Leukosis in Tissue Cultures, Cancer Research **2**:626, 1942.

281. Kirschbaum, A., and Strong, L. C.: Influence of Carcinogens on the Age Incidence of Leukemia in the High Leukemia F Strain of Mice, Cancer Research **2**:841, 1942.

282. McEndy, D. P.; Boon, M. C., and Furth, J.: Induction of Leukemia in Mice by Methylcholanthrene and X-Rays, J. Nat. Cancer Inst. **3**:227, 1942.

leukemia in mice previously treated dermally with methylcholanthrene. A detailed account of the methods and of the histologic observations is presented.

Gardner [283] implanted pellets of estrone (theelin) in 303 mice of the CCB and C3H strains and subsequently observed the development of lymphoid tumors in 25 per cent of these animals. Tumors developed in only 2 per cent of 482 untreated animals. The neoplasms of the treated animals showed distinct predilection for the mediastinum and probably originated in thymus tissue.

Potter and Ward [284] studied the mitochondria of normal and leukemic mouse lymphocytes. They report that these structures appear as small discrete granules in supravital preparations of normal lymphocytes. In spontaneous and transmitted leukemia, the mitochondrial granules appear larger in size.

The leukemoid blood reaction is characterized as a vague category by Meyer and Rotten.[285] According to these authors, two types of reaction have been described. In the first type, although the leukocyte count remains normal or is but slightly elevated, examination of blood films reveals a high percentage of immature granulocytes. Marked leukocytosis is found in the second type of leukemoid reaction, but there is little evidence of granulocytic immaturity. Two cases of gastric carcinoma in which the second type of leukemoid reaction occurred are presented by the authors. Whittemore and Stich [286] observed a leukemoid reaction to sulfadiazine in a 34 year old woman in whom lobar pneumonia developed following an episode of diabetic coma. The leukocytes rose to 90,000 at a time when 37 Gm. of the drug had been administered. Immature granulocytes were noted in the blood film. Following discontinuation of sulfadiazine therapy, recovery occurred.

An unusual case of myeloid metaplasia of the spleen associated with acute hemolytic anemia has been exhaustively discussed by Brewster and Wollenman.[139] The patient, a 25 year old white housewife, complained of weakness and pallor. She appeared icteric, and her spleen was enlarged. Laboratory studies revealed elevated bilirubinemia and hemoglobinemia as well as increased fragility of erythrocytes. The red cell count was 1,000,000 per cubic millimeter. After repeated attempts to demonstrate hemolysis had proved fruitless, splenectomy was performed. After this operation, profound anemia developed, and the patient died. Histologic examination of the spleen revealed many foci of myeloid metaplasia scattered throughout the organ. The authors believe that the spleen had been an important site of erythropoiesis and that its removal precipitated the demise of the patient.

Polycythemia.—A 12 to 15 per cent increase of hemoglobin and erythrocytes was produced in the peripheral blood within a two week period, by the daily administration of 10 mg. of amphetamine sulfate, according to Davis and Harris.[287] No effect was observed on the total leukocyte count, and there was no reticulocyte response. After the administration of the drug was discontinued, the blood values fell promptly to pretreatment levels. A similar rise of the erythrocyte and hemo-

283. Gardner, W. U.: Lymphoid Tumors in Estrogen-Treated Mice, Cancer Research **2**: 725, 1942.

284. Potter, J. S., and Ward, E. N.: Mitochondria in Lymphocytes of Normal and Leukemic Mice, Cancer Research **2**:655, 1942.

285. Meyer, L. M., and Rotten, S. D.: Leukemoid Reaction (Hyperleucocytosis) in Malignancy, Am. J. Clin. Path. **12**:218, 1942

286. Whittemore, W. L., and Stich, M. H.: Leukemoid Reaction to Sulfadiazine, New York State J. Med. **42**:1249, 1942.

287. Davis, J. E., and Harris, A. M.: The Production of Experimental Polycythemia in Man by the Daily Administration of Amphetamine Sulfate, Am. J. Physiol. **137**:94, 1942.

globin levels was observed by Davis [288] following daily injections of solution of posterior pituitary and of epinephrine hydrochloride in both normal and splenectomized rabbits and dogs. Since a significant response occurred in the splenectomized group, the author believes that the phenomenon is not caused by splenic contraction. It is believed that in both the human and the animal experiments these vasoconstrictor drugs cause a state of anoxemia in the marrow which stimulates the production of erythrocytes. Lowenhaupt [289] kept guinea pigs in a low pressure chamber for periods up to three weeks and noted an average increase of 1,000,000 erythrocyte cells per cubic millimeter of blood. He noted a definite rise in reticulocytes shortly after the animals were exposed to reduced oxygen tension, and studies made during this period demonstrated considerable hyperplasia of the marrow. When the animals were released from the chamber, the blood values fell to normal levels, this alteration being preceded by a decrease in the number of reticulocytes. During the period of recovery no increase of serum bilirubin or of tissue iron could be detected.

Although exhaustive experiments have proved beyond a doubt that continuous exposure to anoxia produces an elevation of blood erythrocytes and hemoglobin, relatively little work has been reported on the effect of intermittent exposure to anoxia. Stickney and Van Liere [290] studied the effect of intermittent anoxia on 5 dogs which were subjected to lowered barometric pressures simulating altitudes of 12,000 to 18,000 feet. The animals were placed in low pressure chambers for seven to nine hours daily over a period of six months, and the hemoglobin and red blood cell levels were determined at weekly intervals. The hemoglobin was the first to show an appreciable rise, this being noted first in the third week of the experiment. During the fifth week the erythrocytes showed a definite increase. An average increase of 74 per cent of hemoglobin and 84 per cent of red blood cells was observed by the end of the experimental period. These investigators conclude that intermittent exposure to anoxia is capable of producing a notable degree of acclimatization, proportional to the severity of the anoxia and to the length of time of exposure.

Of 11 patients treated for polycythemia with lead compounds, 9 have been reported by Falconer [291] to show satisfactory results. Repeated intravenous administration of lead phosphate was used. A tendency toward thrombosis constitutes a contraindication for this form of therapy. Lead acetate by mouth was found to be unsatisfactory, since damage to the liver, the central nervous system and the peripheral nerves was observed.

A toxic reaction to sulfonamide therapy occurring in a 61 year old man who had polycythemia vera resulted in anemia, leukopenia and neutropenia, according to Greenwald, Letwin and Spielholz,[292] who found that the polycythemic state returned after the bone marrow recovered from the intoxication. In a short article Rhodes and Grunberg [293] recorded a case of polycythemia vera with a

288. Davis, J. E.: The Production of Experimental Polycythemia by the Daily Administration of Epinephrine or Posterior Pituitary Solution, Am. J. Physiol. **137**:699, 1942.

289. Lowenhaupt, E.: Recovery from Experimental Polycythemia, J. Lab. & Clin. Med. **27**:874, 1942.

290. Stickney, J. C., and Van Liere, E. J.: Erythrocytes and Hemoglobin Values in Acclimatization Produced by Discontinuous Anoxia, J. Aviation Med. **13**:170, 1942.

291. Falconer, E. H.: The Treatment of Polycythemia Vera with Lead Compounds, Am. J. M. Sc. **203**:857, 1942.

292. Greenwald, L.; Letwin, J., and Spielholz, J. B.: Toxic Effect of Sulfanilamide on the Hemopoietic Organs in a Case of Polycythemia Vera, J. A. M. A. **118**:975 (March 21) 1942.

293. Rhodes, A. J., and Grunberg, A.: Polycythemia Vera with Low White Cell Count. Brit. M. J. **1**:553, 1942.

leukocyte count of 5,500 cells per cubic millimeter. The data presented do not seem adequate to establish beyond doubt the diagnosis of Osler-Vaquez disease.

The infrequency of the association of polycythemia vera and thromboangiitis obliterans has been noted by Silbert,[294] who presents his findings in such a case. The author does not believe that there was any cause and effect relation but that the two diseases occurred purely coincidentally. Polycythemia vera complicated by the development of Huntington's chorea was observed by Kotner and Tritt.[295] Multiple cerebral thrombi were believed responsible for the manifestations of involvement of the central nervous system. Fitz, Walker and Branch[296] present a lengthy and rather detailed account of the course of polycythemia vera in a middle-aged physician who was under their observation for several years. This patient was treated with a solution of potassium arsenite (Fowler's solution) and a low iron diet for an extended period with only moderate improvement. Subsequently spray irradiation of the entire body produced an excellent remission. Death eventually occurred, following coronary thrombosis.

Effect of Radioactive Phosphorus in the Treatment of Leukemia, Lymphoblastoma and Polycythemia.—Radioactive phosphorus (P_{32}) has now been employed in the study and treatment of leukemia, lymphoblastoma and polycythemia for three years. Although it is too early to attempt a formal evaluation of the merits and the limitations of this agent, several interesting preliminary surveys of therapeutic results have been published during the year.

Low-Beer, Lawrence and Stone[297] have contributed an excellent general review of the therapeutic use of radioactive phosphorus. The methods of preparation and of administration of this element and a résumé of the results attained in the group of patients studied at the Crocker Institute are included. Two methods of oral treatment have been used. The first consists in administering large doses of radioactive phosphorus (6 to 10 millicuries) by mouth at irregular intervals, whereas the second and more recently developed method consists in giving frequent small doses (0.5 to 3 millicuries) every three days. Further clinical experience will prove which of these therapeutic regimens is the more effective.

Craver[298] points out the fallacy of attempting to treat leukemia, a widely dispersed disease, by means of localized radiation. With the use of roentgen rays of high voltage, much of the disease is left untreated. Spray irradiation of the entire body has proved an advance over older forms of therapy. However, the body's tolerance to this type of treatment is not great enough to enable one to take full advantage of the difference in sensitivity of normal and leukemic tissue. Since radioactive phosphorus is absorbed in high concentration by rapidly growing cancerous tissue, irradiation of the malignant cells is accomplished with a minimum of damage to the normal tissues. Provided that there is evidence of adequate erythropoiesis, Craver administers to his leukemic patient 70 to 150 microcuries of radioactive phosphorus per kilogram in five to seven daily doses. Whenever

294. Silbert, S.: Thrombo-Angiitis Obliterans and Polycythemia Vera, J. Mt. Sinai Hosp. **8**:1021, 1942.

295. Kotner, L. M., and Tritt, J. H.: Chorea Complicating Polycythemia Vera: Report of a Case, Ann. Int. Med. **17**:544, 1942.

296. Fitz, R.; Walker, B. S., and Branch, C. F.: Polycythemia Vera: Report of a Case. Arch. Int. Med. **70**:919 (Dec.) 1942.

297. Low-Beer, B. V. A.; Lawrence, J. H., and Stone, R. S.: The Therapeutic Use of Artificially Produced Radioactive Substances; Radiophosphorus, Radiostrontium, Radioiodine, with Special Reference to Leukemia and Allied Diseases, Radiology **39**:573, 1942.

298. Craver, L. F.: Treatment of Leukemia by Radioactive Phosphorus, Bull. New York Acad. Med. **18**:254, 1942.

deficient erythropoiesis occurs, the dose is reduced to 20 microcuries per kilogram. Thirty-eight patients were treated for leukemia by the author at Memorial Hospital, New York. Of 11 with chronic myelogenous leukemia, 8 were still alive at the time of his report, and satisfactory remission had been produced. Generally, less favorable results were noted in 11 patients who had chronic lymphatic leukemia, whereas no improvement was discerned in 3 who had acute leukemia. One patient with eosinophilic leukemia was benefited by this form of therapy.

Working in the same clinic, Kenney [299] believes that radioactive phosphorus is effective in the treatment of chronic myelogenous leukemia as shown by (1) the reduction of the leukocyte count to, or nearly to, normal, (2) the decrease in splenomegaly, (3) the absence of disturbance in erythropoiesis, (4) the reduction in numbers of myeloblasts and myelocytes in the bone marrow and (5) the absence of radiation sickness. When it was employed in 8 cases of chronic lymphatic leukemia, 5 patients showed definite diminution in size of the spleen and the peripheral lymph nodes whereas only 1 patient demonstrated a decrease in the total leukocyte count. The author urges that caution be used when radioactive phosphorus is administered to patients whose bone marrow is extensively infiltrated, since their tolerance for this form of therapy is poor.

The fractional or small dose regimen of treatment is preferred by Fitz-Hugh and Hodes,[300] who report the results of radioactive phosphorus therapy in 38 patients with assorted diagnoses. Of 8 patients with polycythemia vera so treated, 4 had excellent remission, 2 improved only slightly or not at all, and the other 2 patients were commencing treatment at publication of the report. Of 5 patients with chronic myelogenous leukemia, 2 showed a remission following treatment with radioactive phosphorus. Two of 4 patients with chronic lymphatic leukemia improved after treatment. Only 1 of 5 patients with Hodgkin's disease and 2 of 6 patients with lymphosarcoma showed any response.

Diamond and Warren [301] have treated 12 children for whom a diagnosis of acute leukemia was made. In 3 of them true remissions occurred subsequent to treatment with radioactive phosphorus. Four patients showed slight improvement. In the remaining 5 patients the course of the disease was uninfluenced. Detailed results of the use of radioactive phosphorus in 22 cases of lymphosarcoma are presented by Kenney and Craver.[302] Four of the patients attained excellent remissions of from nine to twelve months. No improvement was discernible in 10 patients. Partial remissions occurred in 4 patients, whereas 2 have had recurrences, which were controlled by further radioactive phosphorus therapy.

Since slight exposure to roentgen rays causes prompt changes in the peripheral blood, Low-Beer and Treadwell [303] were stimulated to study the early hematologic effects of the administration of minute doses of radioactive phosphorus. Using normal human subjects, these authors concluded that 0.006 to 0.009 microcurie of radioactive phosphorus per gram of body weight was sufficient to produce

299. Kenney, J. M.: Radioactive Phosphorus as a Therapeutic Agent in Malignant Neoplastic Disease, Cancer Research **2**:130, 1942.

300. Fitz-Hugh, T., Jr., and Hodes, P. J.: Clinical Experience with Radio-Phosphorus in the Treatment of Certain Blood Dyscrasias, Am. J. M. Sc. **204**:662, 1942.

301. Diamond, L. K., and Warren, S.: Treatment of Leukemia in Children with Radioactive Phosphorus, Am. J. Dis. Child. **64**:958 (Nov.) 1942.

302. Kenney, J. M., and Craver, L. F.: Further Experiences in the Treatment of Lymphosarcoma with Radioactive Phosphorus, Radiology **39**:598, 1942.

303. Low-Beer, B. V. A., and Treadwell, A. deG.: Clinical Studies with the Aid of Radio-Phosphorus: Early Effects of Small Amounts of Radio-Phosphorus on Blood Cell Levels, Uptake and Excretion, J. Lab. & Clin. Med. **27**:1294, 1942.

in the peripheral blood discernible changes, consisting of a transient rise and fall of the platelets and a slight deviation of the red cell and hemoglobin levels in no constant direction.

Erf and Tuttle [304] present further experimental data concerning the fate of radioactive phosphorus in therapeutic doses after its absorption from the intestinal tracts of patients being treated for chronic myelogenous leukemia, chronic lymphatic leukemia and polycythemia vera. Most of the substance remained in the acid-soluble fractions of the erythrocytes, leukocytes and blood plasma during the first ninety-six hours. Radioactive phosphorus appeared early in the nucleoprotein of the erythrocytes and attained a maximum value at the end of the first forty-eight hours after administration, whereas the radioactivity of the phospholipids of the erythrocytes slowly increased during a twenty-one day period. The radioactive phosphorus content of the phospholipid and nucleoprotein fractions of the leukocytes increased only during the first ninety-six hours after ingestion. During the same period the radioactive phosphorus of the phospholipid fraction of the plasma rose, while that of the nucleoprotein fraction decreased.

As the result of extensive studies performed on cyclotron operators, Warren [305] discovered that a few persons show marked fluctuations of their total leukocyte count following only a minimal exposure to the rays emanating from the cyclotron. Such fluctuations indicate instability of the bone marrow and constitute a contraindication to further exposure to the radiation.

Multiple Myeloma.—In their study of 127 cases of multiple myeloma at the Mayo Clinic, Ghormley and his co-workers [306] emphasize the lack of pathognomonic symptoms. Backache was the commonest complaint, followed by weakness and loss of weight. Pathologic fractures occurred in 40.6 per cent of their series. The disease has an average duration of one year after the onset of symptoms. It occurred in males twice as frequently as in females, and the average age of onset was 54 years. Albuminuria occurred in 70 per cent and urinary Bence Jones protein in 68 per cent of these patients. An abnormal serum albumin-globulin ratio was found in a little over half of the cases. The consistent roentgen finding of punched-out areas of bony rarefaction is emphasized. Working in the same clinic, Marisette and Watkins [307] analyzed the hematologic data of 56 cases of multiple myeloma. The most characteristic changes were: (1) anemia of moderate severity and of normochromic type, (2) tightly packed erythrocyte rouleaux, resulting in the so-called greasy blood smear, and (3) accelerated erythrocyte sedimentation. The authors describe the morphologic differences distinguishing myeloma cells from Marschalko plasma cells. Beizer, Hall and Giffin [308] list hyperproteinemia, hypercalcemia, autohemagglutination, Bence Jones proteinuria, retention of nitrogen and an anticomplementary reaction of the blood serum as important but not pathognomonic laboratory findings of multiple myeloma. The value of aspirated sternal marrow as an aid to diagnosis is emphasized. Although life insurance statistics state that multiple myeloma comprises 0.03 of 1 per cent of all tumors,

304. Erf, L. A., and Tuttle, L. W.: Phosphorus Metabolism of Blood of Patients with Leukemia and Polycythemia, Am. J. M. Sc. **203**:83, 1942.

305. Warren, S.: Blood Findings in Cyclotron Workers, Radiology **39**:194, 1942.

306. Ghormley, R. K.; Pollock, G. A.; Hall, B. F., and Beizer, L. H.: Multiple Myeloma, Surg., Gynec. & Obst. **74**:242, 1942.

307. Marisette, L., and Watkins, C. H.: Multiple Myeloma: Diagnostic Value of the Blood Smear, Proc. Staff Meet., Mayo Clin. **17**:433, 1942.

308. Beizer, L. H.; Hall, B. E., and Giffin, H. Z.: The Diagnosis of Multiple Myeloma by Sternal Aspiration, Am. J. M. Sc. **203**:829, 1942.

Preston [309] believes its incidence to be considerably higher than is indicated by these figures. A short case history is included in his article. Haines [310] presents a case of myeloma which developed in the pharyngeal tonsil of a 75 year old farmer.

BONE MARROW

The sternal marrow of 40 healthy adults was examined by Plum,[311] who records the average percentage distribution of the various stages of leukocytes and erythrocytes found. A description of the cells normally found in marrow is included. Reich and Kolb,[312] studying 26 normal persons, performed simultaneous punctures at two sites on the sternum and made counts of the elements found, using Wright's stain. Since considerable variation occurred in their results, the authors conclude that quantitative determination of marrow cells is inexact. Davidson, Davis and Innes [33] review two opposing theories of the erythropoiesis in pernicious anemia. The first theory is that the megaloblastic erythropoiesis of pernicious anemia is quite distinct from normoblastic erythropoiesis, whereas the second hypothesis contends that the megaloblastic marrow of that disease results from arrest of maturation and subsequent disappearance of the more mature erythrocytic elements from the marrow. In their studies of 12 cases of pernicious anemia, the authors observed prompt transformation of the marrow within six to ten hours after the initial injection of liver extract. Megaloblasts decreased in number while early normoblasts increased abruptly. No evidence of increased mitosis was noted. These investigators believe that their data support the theory that arrest of maturation occurs. On the other hand, Wilson,[313] who made somewhat similar studies on 2 patients, concludes that liver therapy prevents the further development of abnormal megaloblasts and permits normoblastic erythropoiesis to proceed. In observations of the marrow in cases of iron deficiency anemia, this author has found evidence that administration of iron stimulates all stages of erythrocytic maturation.

Beizer and Watkins [186] report that in 12 cases of aplastic anemia death occurred only in those in which the marrow showed marked depression of hemopoietic activity and relative lymphocytosis. In cases in which the marrow was hyperplastic, recovery was the rule. Mandell, Meranze and Meranze [314] discuss the bone marrow in various common types of blood dyscrasia from the standpoint of morphology.

The importance of aspiration of sternal marrow as a diagnostic aid in cases of multiple myeloma is emphasized by Beizer, Hall and Giffin,[308] who were able to verify the diagnosis in 8 of their 10 cases by this procedure.

An unusual case of fatal asthma is presented by Chafee, Ross and Gunn,[315] in which 22 per cent of the nucleated marrow cells were eosinophilic granulocytes. Eosinophilic infiltration of the lungs and of the myocardium was also described.

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309. Preston, E. P.: Multiple Myeloma, J. Florida M. A. **29**:82, 1942.

310. Haines, M.: A Metastasizing Plasma-Cell Tumor of the Pharyngeal Tonsil, J. Laryng. & Otol. **57**:264, 1942.

311. Plum, C. M.: The Composition of the Bone Marrow in Normal Adults: The Cells of the Bone Marrow, Acta med. Scandinav. **107**:11, 1941.

312. Reich, C., and Kolb, E. M.: A Quantitative Study of the Variations in Multiple Sternal Marrow Samples Taken Simultaneously, Am. J. M. Sc. **204**:496, 1942.

313. Wilson, T. E.: The Bone Marrow in Anaemia, M. J. Australia **1**:513, 1942.

314. Mandell, T. H.; Meranze, D. R., and Meranze, T.: The Clinical Value of Sternal Bone Marrow Puncture, Ann. Int. Med. **16**:1180, 1942.

315. Chafee, F. H.; Ross, J. R., and Gunn, E. M.: Eosinophilia in Fatal Asthma: Studies of Bone Marrow and Myocardium, Ann. Int. Med. **17**:45, 1942.

Blood containing malarial parasites was injected intrasternally into 9 uninfected persons in the experiments of Quattrin.[316] The parasites disappeared from the marrow within three hours after injection and could not be demonstrated in reticuloendothelial cells or in myelocytes. Clinical malaria developed in 6 of the subjects after an incubation period of nine days, a period longer, the author believes, than that usually noted after intravenous injection and suggesting that the marrow exerts some unknown action which delays the onset of clinical symptoms.

Employing aqueous extracts of rabbit marrow, Nettleship[317] produced in guinea pigs a rabbit myelocyte antiserum which when administered intravenously to rabbits caused prompt significant neutropenia in their peripheral blood. Postmortem examination of the experimental animals demonstrated hyperemia, petechiae and actual necrotic areas in the marrow. The spleen was uniformly enlarged.

316. Quattrin, N.: Richerche sull, inoculazione del parasita malarico per via intramidoliare, Riv. di malariol. **20**:229, 1941.

317. Nettleship, A.: Bone Marrow Changes Produced by Specific Antibodies, Am. J. Path. **18**:689, 1942.

(*To Be Concluded*)

Book Reviews

A Manual of Clinical Therapeutics: A Guide for Students and Practitioners. By Windsor C. Cutting, M.D. Price, $4.00. Pp. 609. Philadelphia: W. B. Saunders Company, 1943.

The title presents concisely the contents and purpose of this book. The diseases and symptom complexes discussed include almost everything encountered by a general practitioner that requires drugs and allied procedures for its proper management. The book is relatively small, small enough that it can be easily carried in the pocket or medical bag. It includes a brief presentation of definite procedures that are to be used for each clinical state without discussing their advantages or disadvantages. The therapeutic recommendations are brief and to the point. As would be expected, a satisfactory use of this book requires a thorough knowledge on the part of the reader of therapeutics, pharmacology, physiology and clinical medicine. A physician with this knowledge can benefit considerably from the use of this book, for he can appreciate the reasons for the procedures recommended and understand the incompleteness of some of the discussions. For example, the discussion of the "Care of the Teeth and Gums" is presented by the author in three sentences: "The teeth should be brushed daily, preferably at bedtime. Dentifrices are cosmetic preparations which promote the use of a toothbrush and may otherwise aid cleansing the teeth. Tooth powders and pastes are equally satisfactory." Prescriptions for two inexpensive dentifrices are then suggested. Obviously, this is a summary of the care of the teeth and gums as practiced by many persons, but it is a far from adequate presentation of the whole problem of dental care, an extremely important and neglected therapeutic problem. Nevertheless, such examples do not detract from the value of the book when it is used intelligently by well trained physicians as a source of concise, ready information. The diet lists, lists of poisons and antidotes, weight and growth charts, rules for dosages and other aspects of the writing of prescriptions, lists of clinical laboratory procedures, with the values of the normal variations, quantitative methods for controlling drug therapy, lists of drugs, with doses, and bibliography are among the other good features of the book. The author has limited the drugs and procedures recommended to those accepted by the Pharmacopeia of the United States, the National Formulary and New and Nonofficial Remedies.

For persons who want concise and ready information on therapeutics, the book rates highly among any of its sort. The material is indexed satisfactorily, and the data are easily found.

Vascular Spasm: Experimental Studies. By Alexander John Nedzel, M.D. Price, $2.75. Pp. 151, with 161 figures. Urbana, Ill.: The University of Illinois Press, 1943.

Nedzel presents a summary of his experimental work on vascular spasm. He believes that a great number of diseases are due to disturbances brought about in an organ as a result of vascular spasm. Following the spasm of blood vessels, there results anoxia with associated local disturbances in metabolism and if prolonged permanent physiologic and anatomic damage. Endocarditis, gastric ulcer and multiple sclerosis are among the disease states discussed. The author presents evidence of having produced these states, or their equivalents, in experimental animals by vasospasm, pitressin having been the vasconstricting agent used.

The reviewer is impressed by the lack of thoroughness of control studies and the rather sweeping clinical implications made as a result of artificial experimental observations. Graphs are presented in the chapter entitled "Splanchno-Peripheral Balance" to show how application of cold to the surface of the body produces a decrease in the temperature of the viscera and heat a rise in visceral temperature. In practically all instances there is relatively little time allowed for the reaction from one stimulus to wear off before the other is applied. One is impressed by the fact that the rise in visceral temperature after the cold stimulus is removed is not due to the heat applied shortly after the removal of the cold stimulus but a result of the mere removal of the cold stimulus. In every experiment illustrated graphically, cold was the first stimulus used. The author did not isolate culturally and identify precisely injected organisms which were "made" to lodge in certain tissues, e. g. the mitral valves, because of previous injury by vascular spasm. In spite of such criticisms the monograph should prove of interest to investigators engaged in the studies of vascular physiology and the effects of climate on the mechanism of disease.